

AMINOMETHYLENEMALONATES AND THEIR USE IN HETEROCYCLIC SYNTHESIS

István Hermecz
Geza Kereszturi
Lelle Vasvari-Debreczy

**Aminomethylenemalonates and Their Use in
Heterocyclic Synthesis**

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Preface

Volume 54 of *Advances in Heterocyclic Chemistry* is a monograph volume, i.e., it is devoted to a single subject, the aminomethylenemalonates.

Aminomethylenemalonates are of great importance in heterocyclic synthesis and have been used in the preparation of a very wide variety of heterocycles. The chemistry of this group of compounds has not been reviewed in more than 50 years. The present treatment by István Hermecz and colleagues, Geza Karesztúri and Lelle Vasvári-Debreczy, provides a comprehensive overview.

After an introductory section, work from the 19th century is briefly considered and subsequent sections discuss in turn the structure and physicochemical properties of the aminomethylenemalonates, their preparation, and, in the largest sections, the application of the aminomethylenemalonates to heterocyclic synthesis.

The large literature on cyclization reactions of aminoalkylidenemalonates is surveyed in order of the various ring systems that are formed. Of particular importance are the preparations of 4-hydroxyquinoline derivatives and of the corresponding naphthyridines. But a wide variety of other bicyclic heterocycles has also been prepared by methods of this type, as have tri- and polycyclic analogs.

An appendix systematically lists references to reactions of dialkylalkoxymalonates with amines, including not only the common aliphatic and aromatic amines, but also a very wide variety of heterocyclic amines classified according to ring system. The appendix also provides systematic references to the different ring systems obtained by ring closure of the dialkylaminomethylenemalonates. The appendix should be used in conjunction with the subject index; a separate subject index is provided for this monograph volume.

A. R. KATRITZKY

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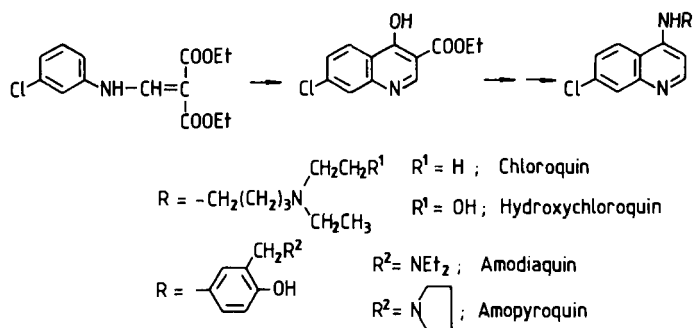
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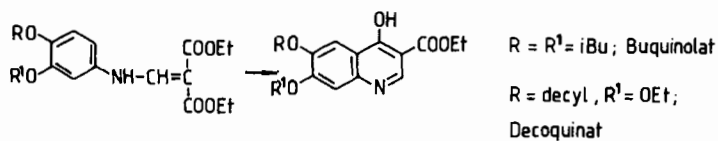
Introduction

Research to produce effective antimalarial agents was at the focus of medicinal chemistry in the early 1940s (46MI1), while the search for anticcoidal quinolines was very active in the 1970s (88MI10). The discovery in 1962 of nalidixic acid, a new type of antibacterial agent, initiated intense international competition to synthesize more effective agents with broader spectrums (77MI1). These research efforts led to the appearance of the third generation of nalidixic acids: norfloxacin and pefloxacin and others (88MI8).

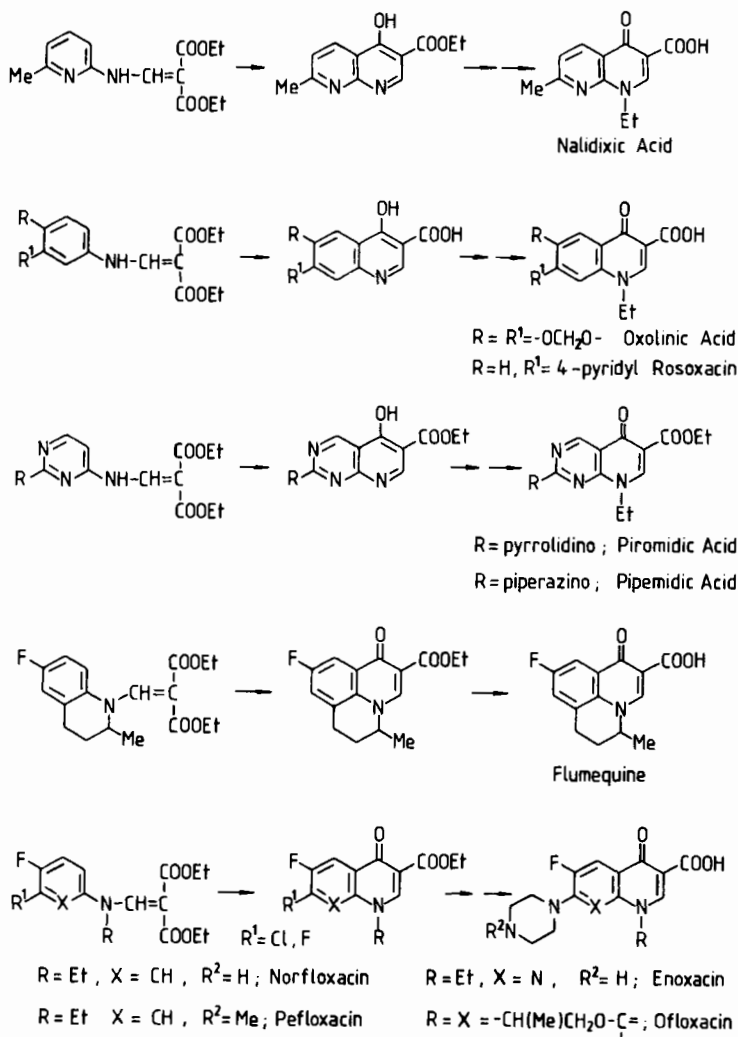
The aim of this review is to survey the chemistry and, in particular, the use in heterocyclic synthesis of aminomethylenemalonates (**1**) and their cyclic esters (**2**), where R¹ and R² or R² and R³ may likewise form a ring. Some early reviews in this field merely touched on certain aspects of the chemistry of aminomethylenemalonates and did not treat the subject systematically (48CRV43).



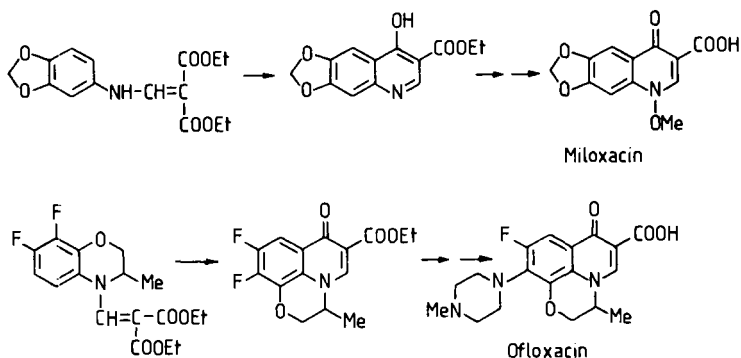
SCHEME 1



SCHEME 2

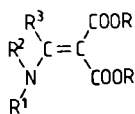


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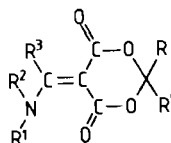


SCHEME 3 (continued)

The primary chemical literature has been surveyed up to the end of 1990. *Chemical Abstracts* subject and chemical substance indexes have been searched up to and including Volume 110. References appeared in Volumes 111 and 112 and a few more references from the later literature have been added to the Appendix (Chapter 7, Section D).



(1)



(2)

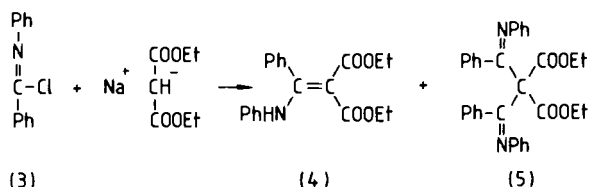
After the introductory section, work from the 19th century is briefly considered. The subsequent sections discuss in turn the structure and physicochemical properties of aminomethylenemalonates (1 and 2), syntheses, the cyclization of the title compounds, and other reactions of aminomethylenemalonates.

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CHAPTER 2

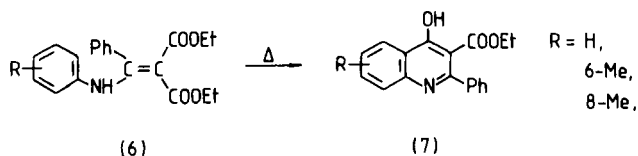
Work in the Nineteenth Century

The first derivative (4) of aminomethylenemalonates (1) was prepared in 13% yield by Just through the reaction of diethyl sodiomalonate and imidoyl chloride (3) in diethyl ether (1885CB319, 1885CB2623). Disubstituted malonate (5) was also isolated from the reaction mixture in 9% yield.

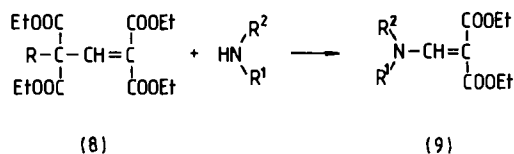


Imidoyl chlorides of toluidines and naphthylamines were also applied (1886CB979). To avoid the formation of the disubstituted malonates, 2 mol of sodiomalonate was reacted with 1 mol of imidoyl chlorides (1886CB979).

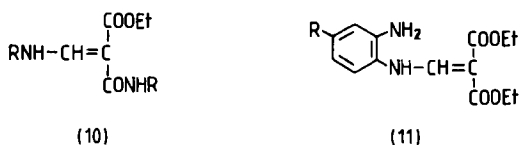
When diethyl (arylamino)phenylmethylenemalonates (6) were heated in aqueous hydrochloric acid, only acetophenone and the corresponding amine were obtained (1885CB2623; 1886CB979), but quinoline-3-carboxylates (7) were the products in the melt when 6 was heated to above 150°C (1885CB2632; 1886CB1541).



Ruhemann *et al.* obtained diethyl aminomethylenemalonates (9) in the reactions at ambient temperature of diethyl diethoxycarbonylglutaconate (8, R² = H) with aqueous ammonia, primary and secondary aliphatic amines and diamines, benzylamine, piperidine, aniline, and aromatic diamines (1891JCS743; 1892JCS791; 1894CB2743; 1895CB822; 1897CB2022). At higher temperatures, or during a longer reaction period, one of the ester groups in 9 also reacted with amines to give a malonamate derivative (10) (1892JCS791; 1894CB2743).



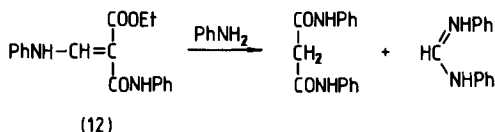
In *o*-phenylenediamines, only one of the amino groups reacted with compound **8** ($\text{R} = \text{H}$) to give *N*-(2-aminophenyl)aminomethylenemalonates (**11**, $\text{R} = \text{H}$), whereas both amino groups in *m*- and *p*-phenylenediamines reacted (1895CB822; 1897CB2022).



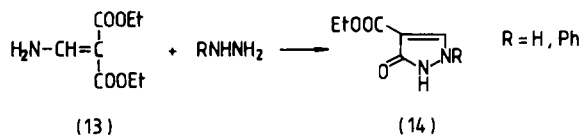
Aminomethylenemalonate (**9**, $\text{R}^1 = \text{R}^2 = \text{H}$) was prepared from the benzyl derivative of diethoxycarbonylglutaconate (**8**, $\text{R} = \text{PhCH}_2$) with ammonia (1891JCS743). Depending on the reaction conditions, Gutzzeit and Band also prepared aminomethylenemalonates (**9**, $\text{R}^1 = \text{H}$, Ph ; $\text{R}^2 = \text{H}$) and their monoamides (**10**, $\text{R} = \text{H}$, Ph), in addition to the corresponding malonamide, by using aqueous ammonia and aniline (1895LA108; 1897CB1757).

When diethyl aminomethylenemalonate (**9**, $\text{R}^1 = \text{R}^2 = \text{H}$) was reacted with aqueous ammonia at 100°C in a closed tube, malonamide was obtained. Decomposition of **9** ($\text{R}^1 = \text{R}^2 = \text{H}$) also occurred on the action of boiling aqueous barium hydroxide (1892JCS791).

The reaction of diethyl aminomethylenemalonate (**9**, $\text{R}^1 = \text{R}^2 = \text{H}$) and aniline gave a mixture of *N*-phenylaminomethylenemalonamate (**12**) and malonanilide (1894CB2743). When phenylaminomethylenemalonamate (**12**) was reacted for a prolonged time with aniline, malonanilide and *N,N'*-diphenylformamidine were obtained (1894CB2743).



The reaction of diethyl aminomethylenemalonate (**13**) with hydrazines afforded pyrazolonecarboxylates (**14**) (1894CB2743).

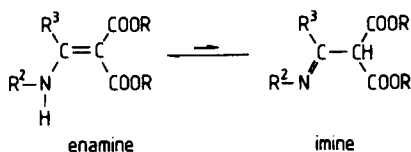


In 1897, Claisen and Haase prepared amino- and *N*-phenylaminomethylenemalonates (**9**, $\text{R}^1 = \text{H}, \text{Ph}$; $\text{R}^2 = \text{H}$) in the reactions of diethyl ethoxymethylenemalonate (EMME) with ammonia and aniline (1897LA75). This reaction and its "one-pot" version later became the basic synthetic methods for preparing aminomethylenemalonates (**1**) (see Sections IV,A,1 and IV,A,2).

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Structure of Aminomethylenemalonates

The aminomethylenemalonates (**1** and **2**) may exist in imine or enamine tautomeric forms of R^1 or R^2 is a hydrogen atom. In some early papers, the imine tautomer (see below) was given for the structure of the products, usually without any explanation or evidence (e.g., 1885CB319; 37JCS867; 49JIC171; 88KGS931).

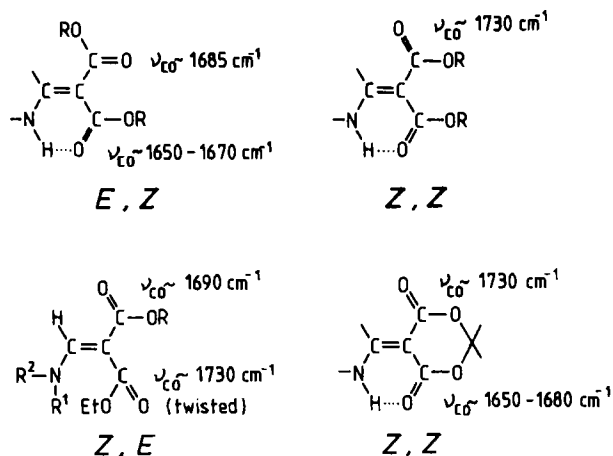


Since 1960, almost all papers have provided at least some spectroscopic evidence that these compounds (**1** and **2**) exist as the enamine tautomer in solid phase or in solution. Imine tautomers have been detected for only those aminomethylenemalonates in which R^2 and R^3 formed a ring (e.g., 83IZV1687, 83MI2; 88ZOR1793). This chapter will examine only certain papers in which details of spectroscopic investigations or quantum-chemical calculations are given.

The lowest-energy UV maximum of aminomethylenemalonates (**1** and **2**) appears above 280 nm; it may be assigned to the $\pi-\pi^*$ transition (e.g., 69JA6683; 76ACH91; 78MI5, 78T2321; 79JST77). Uray *et al.* determined empirical additive group constants to predict the UV maxima of aminomethylenemalonates (**1** and **2**) (79JST77).

Infrared investigations on *N*-monosubstituted aminomethylenemalonates (**1**, R^1 or $R^2 = H$) have revealed that the conformation *E,Z* is preferred in crystal lattices, whereas in solutions in nonpolar solvents, these compounds exist as the conformations *E,Z* and *Z,Z* in temperature- and concentration-dependent equilibria [79JCS(P2)1376; 81JCS(P2)561; 87JCS(P2)301]. These conformations can be distinguished via the carbonyl frequencies in their spectra (see Scheme 4). In the solid state, these compounds sometimes adopt the *Z,Z* conformation, in which a strong coupling may exist between the two carbonyl groups. This is indicated by a frequency separation of 50–60 cm^{-1} .

The IR spectra indicated that in the *N,N*-disubstituted derivatives, the *Z,E* form is more likely both in solid state and in solution [73JCS(P2)657;



SCHEME 4

79JCS(P2)1376]. In this conformation, the *cis*-carbonyl is usually twisted from the plane of the C=C bond and the *trans*-carbonyl group. Data on the Raman spectra of aminomethylenemalonates were also presented in some papers [79JCS(P2)1376; 81JCS(P2)561; 87JCS(P2)301].

In the ^1H -NMR spectra, the signal of the vinyl proton in compounds **1** and **2** ($\text{R}^3 = \text{H}$) may appear in the range 7.2–8.5 ppm for *N*-unsubstituted and *N*-alkyl-substituted aminomethylenemalonates (**1** and **2**) [e.g., 69JA6683; 73IZV2013; 74OMR240; 78T2321; 79JST77, 79RRC1143; 81JCS(P2)561; 88JCS(P1)863, 88JCS(P1)869] and in the range 7.8–9.5 ppm for *N*-(het)aryl-substituted aminomethylenemalonates (**1** and **2**) [e.g., 67TL2957; 71JOC219; 76ACH91; 79JHC1021, 79JST77, 79RRC1143; 81JCS(P2)561; 83BSF66; 88JCS(P1)863, 88MI13; 89CCC713, 89MI3].

In the *N*-monosubstituted aminomethylenemalonates (**1** and **2**; $\text{R}^1 = \text{H}$), a relatively strong intramolecular hydrogen bond exists between the NH group and the oxygen atom of the *cis*-carbonyl group. The chemical shift of the NH group appears between 9.1 and 9.7 ppm for compounds in which R^2 is an alkyl or aralkyl group [e.g., 79RRC1143; 81JCS(P2)561; 87JCS(P2)301; 88JCS(P1)863] and appears above 10.0 ppm for compounds in which $\text{R}^2 = (\text{het})\text{aryl}$ [e.g., 67TL2957; 71JOC219; 78MI5; 79JHC1021; 81JCS(P2)561; 87JCS(P2)301].

The high coupling constant $^3J_{\text{NH}, \text{CH}} \approx 13 \text{ Hz}$ indicates the *trans* orientation of the hydrogen bonded to the amino group and the vinylic hydrogen [e.g., 67TL2957; 71JOC219; 79JHC1021, 79JST77, 79RRC1143; 81JCS(P2)561; 87JCS(P2)301]. The coupling constant $^1J_{15\text{N}-\text{H}}$ points to an

extensive n, π -interaction between the nitrogen lone pair and the $C=C$ double bond in aminomethylenemalonates (Table I) (67T1489).

Some papers contain ^{13}C -NMR data [e.g., 78IZV2301; 80CB2545; 88JCS(P1)863, 88JCS(P1)869, 88MI13; 89CCC713, 89MI3], ^{13}C CP-MAS NMR data in the solid state (89MI3), and mass spectral data [e.g., 79JHC1021, 79RRC1143; 88JCS(P1)863, 88JCS(P1)869] on aminomethylenemalonates. Extensive dynamic ^1H -NMR studies on aminomethylenemalonates revealed the existence of enhanced energy barriers to rotation around the $C-N$ bond [e.g., 67TL3259; 68TL5923; 69JA6683; 73IZV2013; 74OMR240; 78ACS(B)421, 78T2321; 80CB2545; 88JCS(P1)869] and an associated reduction of the energy of rotation around the $C=C$ bond (see Table II). Both energy barriers are extremely sensitive to the nature of group R^3 .

The activation energy data suggest that the isomerization around the $C=C$ bond occurs in a dipolar rather than a biradical transition state.

In the ground state, aminomethylenemalonates possess an essentially planar geometry, which maximizes the electron delocalization in the molecules. In the heteropolar transition state, the plane of the groups R^3 and NR^1R^2 and the plane of the two carbonyl groups occupy orthogonal positions. More details of the dynamic and static stereochemistry of push-pull ethylenes, as in compounds **1** and **2**, are discussed in two excellent reviews (73TS295; 83TS83).

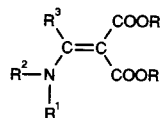
The heteropolar transition state was also predicted by semiempirical quantum-chemical calculations (78T2315). The ground-state properties of

TABLE I
 ^{15}N -NMR DATA ON AMINOMETHYLENEMALONATES^a

| R | $\delta_{^{15}\text{N}}$ (ppm) | | $^1J_{^{15}\text{N}-\text{H}(\text{Hz})}$ | | $^3J_{\text{H}(\text{C})-\text{H}(\text{C})\text{H}(\text{C})}$ | References |
|----|--------------------------------|-------------------|---|-------------------|---|------------|
| | CDCl_3 | $\text{DMSO}-d_6$ | CDCl_3 | $\text{DMSO}-d_6$ | CDCl_3 | |
| H | 275.4 | 269.6 | 93.5 | | 15.7 | 86ZC404 |
| Ph | 251.8 | 251.8 | 91.9 | 92.7 | | 86ZC404 |
| Ph | | | 91.4 ± 0.2 | | 13.7 | 67T1489 |

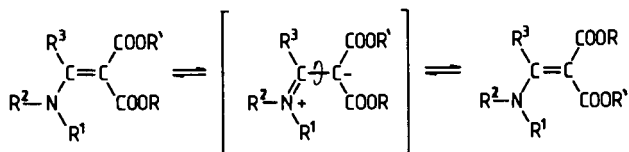
^a $\text{Me}^{15}\text{NO}_2$ was used as an external standard.

TABLE II
FREE-ENERGY BARRIERS TO ROTATION ABOUT THE C=C AND C—N BONDS OF AMINOMETHYLENEMALONATES



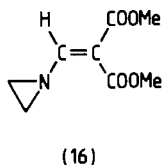
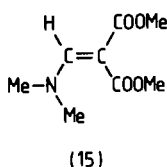
| | R | R ¹ | R ² | R ³ | >C=C< $\Delta G^\ddagger(\text{kJmol}^{-1})$ | >N-C= $\Delta G^\ddagger(\text{kJmol}^{-1})$ | Solvent | References |
|----------------|---------------------|------------------------------------|----------------|----------------|---|--|----------------------------------|--------------------|
| $\vec{\Sigma}$ | Et | H | H | H | 93.5 ± 2.5(OCH ₃) 90.0 ± 2.5(CH ₃) | — | DMSO- <i>d</i> ₆ | 85ZC287 |
| | Et | H | Pr | H | 86.2 ± 2.5(OCH ₃) 84.2 ± 2.5(CH ₃) | — | DMSO- <i>d</i> ₆ | 85ZC287 |
| | Me | Me | Me | H | 65.3 | 55.7 | CH ₂ Cl ₂ | 67TL3259 |
| | | | | | 66.2 ± 1.7 | 54.0 ± 0.84 | CH ₂ Cl ₂ | 78T2321 |
| | | | | | 52.00 ± 0.13 | 55.10 ± 0.41 | CD ₃ OD | 73IZV2013;74OMR240 |
| | | | | | 63.89 ± 0.17 | 55.23 ± 0.41 | CDCl ₃ | 73IZV2013;74OMR240 |
| | Et | Me | Me | H | 66.99 | 54.43 | CH ₂ Cl ₂ | 67TL3259 |
| | >C(Me) ₂ | Me | Me | H | — | 85.9 ± 1.2 | Ph ₂ O | 80CB2545 |
| | Me | Et | Et | H | 59.87 ± 2.5 | 55.27 ± 0.84 | CH ₂ Cl ₂ | 78T2321 |
| | Me | <i>i</i> Pr | <i>i</i> Pr | H | 54.01 ± 1.7 | 55.27 ± 0.84 | CH ₂ Cl ₂ | 78T2321 |
| | Me | —(CH ₂) ₂ — | | H | 97.14 | 30.57(a) | C ₄ Cl ₆ | 78T2321 |
| | Me | —(CH ₂) ₃ — | | H | 80.39 ± 2.51 | 60.29 ± 0.84(a) | 1-Chloro-naphthalene | 78T2321 |
| | Me | —(CH ₂) ₄ — | | H | 73.27 ± 1.68 | 60.29 ± 0.84(a) | C ₆ H ₅ Br | 78T2321 |
| | Me | —(CH ₂) ₅ — | | H | 61.13 ± 2.51 | 51.08 ± 0.84 | CH ₂ Cl ₂ | 78T2321 |

| | | | | | | | |
|----|--------------------|-------------------------------------|------------------|--|------|---|------------------------|
| Me | Me | Me | Me | 38.1 | 36.4 | CH ₂ Cl ₂ , (CD ₃) ₂ CO | 69JA6683, 69JA6689 |
| Me | Me | Me | SMe | 25 39.4(OMe) | 42.5 | CHCl ₂ F (CD ₃) ₂ CO, PhMe, CH ₂ Cl ₂ (CD ₃) ₂ CO | 78ACS(B)421 69T4649 |
| Me | Me | Me | NMe ₂ | 37.2(NMe ₂) — | 58.6 | CHCl ₂ F | 69T4649 |
| Me | H | Ph | H | 92.9 ± 1.0 | | DMSO- <i>d</i> ₆ | 78ACS(B)421 |
| | | | | 83.32 | | PhCN | 83BSF66 |
| Et | H | Ph | H | 93.9 ± 2.0(OCH ₂), 92.9 ± 1.5(CH ₃) 82.9 | | DMSO- <i>d</i> ₆ | 85ZC287 |
| Et | H | 3-EtO 4-AcOPh | H | 81.65 | | C ₆ D ₅ NO ₂ C ₆ D ₅ NO ₂ | 76ACH91 76ACH91 |
| Me | Me | Ph | H | 81.23 71.04 | | CHBr ₃ PhCN | 67TL3259 83BSF266 |
| Me | Me | Ph | Me | 41.87 | | (CD) ₃ CO | 69JA6683, 69JA6689 |
| Me | Me | 4-MeOPh | H | 77.46 | | CHBr ₃ | 67TL3259 |
| Me | Me | 4-NO ₂ Ph | H | 92.53 | | CHBr ₃ | 67TL3259 |
| Me | H | Ph | SMe | 50.24 | | CH ₂ Cl ₂ | 69T4649 |
| Me | Me | Ph | SMe | 35.6 | | (CD ₃) ₂ CO | 69T4649 |
| Me | Me | 4-NO ₂ 2Ph | SMe | 41.5 | | (CD ₃) ₂ CO | 69T4649 |
| Me | Me | —(CH ₂) ₃ — | | 41.03 | | (CD ₃) ₂ CO | 69JA6683 |
| Me | CH ₂ Ph | —(CH ₂) ₃ — | | 41.87 | | (CD ₃) ₂ CO | 69JA6683 |
| Me | Ph | —(CH ₂) ₃ — | | 57.36 | | (CD ₃) ₂ CO | 69JA6683, 69JA6689 |
| Me | H | —CH ₂ CH ₂ S— | | 93.4 | | PhMe | 69T4649 |
| Me | Me | —CH ₂ CH ₂ S— | | 39.4 | | PhMe | 69T4649 |



SCHEME 5A

compounds **15** and **16** were calculated by the INDO method (78T2315) (see Table III) in terms of the structure and charge population of the transition state for rotation about the C=C bond. The calculated ground-state properties of **15** were in agreement with experimental results [73JCS(P2)657; 80IZV402], and the calculated properties of the transition state for rotation about the C=C bond were also found to be similar in ^2H -NMR experiments.



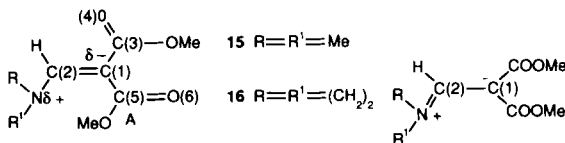
During the rotation about the N—C= bond, the interaction between the nitrogen lone pair and the rest of the molecule is destroyed, and the nitrogen atom adopts a pyramidal configuration. In the transition state for rotation about the N—C bond, the nitrogen lone pair and the C=C double bond system occupy orthogonal positions.

The π -electron density and charge distribution of some aminomethylenemalonates have been estimated via semiempirical quantum-chemical calculations (72ACH281; 78IZV2301; 79RRC1143). X-Ray crystallographic studies indicated a nearly planar structure of *N,N*-dimethylaminomethylenemalonate (**15**); the nitrogen atom was planar and the *cis*-carboxyl group was twisted from the main molecular plan [73JCS(P2)657]. Some bond lengths are tabulated in Table III.

The tautomerism of 2-pyridylmalonate, 2-pyrazinylmalonate, 3-pyridazinylmalonates (**17**), 2-pyrimidinylmalonates, 4-pyrimidinylmalonates (**18**), (1,3,5-triazin-2-yl)malonates was studied by Petrenko and Mamaev *et al.*

TABLE III

GEOMETRIC AND CHARGE POPULATION DATA ON THE GROUND STATE AND TRANSITION STATE TO ROTATION ABOUT C(2)=C(1) OF AMINOMETHYLENEMALONATES (**15** AND **16**)



| Bond length(pm) | Ground State | | | Transition State | |
|------------------------------|-------------------------------------|-------------------------------------|---|-------------------------------------|---|
| | $R = R' = Me$ Expt. ^a | $R = R' = Me$ Calc. ^b | $R = R' = (CH_2)_2$ Calc. ^c | $R = R' = Me$ Calc. ^c | $R = R' = (CH_2)_2$ Calc. ^c |
| C(2)-C(1) | 138.0(5) [136.5(4)] | 137 | 136 | 142 | 139 |
| N - C(2) | 133.7(4) [133.6(4)] | 132 | 137 | 132 | 135 |
| C(1)-C(3) | 144.3(4) [146.6(4)] | | | | |
| C(3)-C(4) | 122.3(5) [120.6(3)] | | | | |
| C(1)-C(3) | 148.7(5) [147.4(4)] | | | | |
| C(5)-O(6) | 120.0(5) [120.4(4)] | | | | |
| Conformation of C(5)O(6) (A) | Twisted(67°) | Twisted(67°) | Co-planar | Co-planar | Co-planar |
| Configuration of N | Planar | Planar | Nonplanar | Planar | Planar |
| π charge on N | | +0.290 | | +0.494 | +0.492 |
| π charge on C(1) | | +0.142 | +0.167 | +0.350 | +0.348 |
| π charge on C(2) | | +0.251 | +0.196 | +0.527 | +0.532 |
| π charge on C(3) | | +0.214 | +0.211 | +0.217 | +0.219 |
| π charge on O(4) | | -0.434 | -0.417 | -0.511 | -0.480 |

| Bond order between | Ground State | | | Transition State | |
|--------------------|------------------------|------------------------|------------------------------|------------------------|------------------------------|
| | $R = R' = Me$ Expt. | $R = R' = Me$ Calc. | $R = R' = (CH_2)_2$ Calc. | $R = R' = Me$ Calc. | $R = R' = (CH_2)_2$ Calc. |
| N - C(2) | | 0.505 [(0.49)] | 0.429 ^d | | |
| C(2)-C(1) | | 0.787 [(0.80)] | 0.802 | | |
| C(1)-C(3) | | 0.358 | 0.327 | | |
| C(3)-O(4) | | 0.802 | 0.794 | | |

^a 73JCS(P2)657; [78IZV402].^b 78T2315; [79RRC1143].^c 78T2315.^d π -Bond order with a co-planar aziridino group.

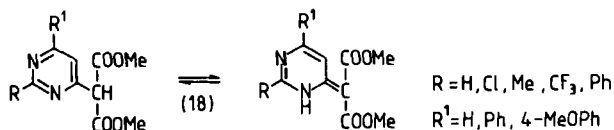
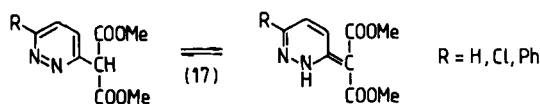
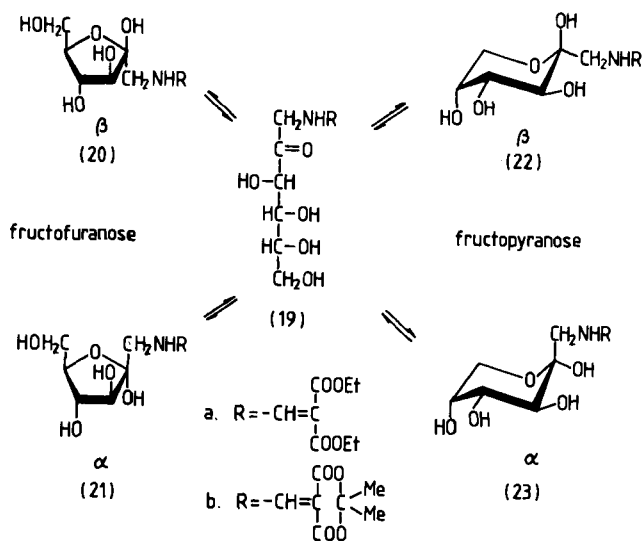


TABLE IV
EQUILIBRIUM MIXTURE OF (1-DEOXY-D-FRUCTOSEAMINO)METHYLENE-MALONATES (19)
(SCHEME 5)

| Solvent | Malonate | β -Furanose (20) % | α -Furanose (21) % | β -Pyranose (22) % | α -Pyranose (23) % |
|------------------------------------|----------------|--------------------------------|---------------------------------|--------------------------------|---------------------------------|
| D ₂ O | Diethyl | 10 | 15 | | 74 |
| (CD ₃) ₂ SO | Diethyl | 40 | 28 | 10 | 22 |
| D ₂ O | Isopropylidene | 14 | 16 | | 70 |



SCHEME 5B

(77KGS395; 83IZV1687, 83MI2; 84KGS827, 84KGS832; 88KGS241, 88ZOR1793, 88ZOR1799, 88ZOR1806).

(1-Deoxy-D-fructosamino)methylenemalonates (**19**) exhibited a solvent-dependent equilibrium involving several cyclic isomeric forms (**20–23**) (see Scheme 5B and Table IV) (86MI10).

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Syntheses

A. Syntheses of Dialkyl 1-Aminoalkylidenemalonates

1. FROM AMINES AND DIALKYL 1-ALKOXYALKYLIDENEMALONATES

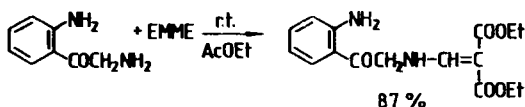
The reactions of amines and dialkyl alkoxymethylenemalonates are most frequently used to prepare the aminomethylenemalonates. Dialkyl alkoxy-methylenemalonates react smoothly with amines under a wide variety of reaction conditions, usually with high yields (Scheme 6). The reactions probably proceed by an addition–elimination mechanism. In some cases, the addition products have been successfully isolated.

When 3-amino-5-methylthio-1,2,4-triazole was reacted with diethyl ethoxymethylenemalonate (EMME) in aqueous ethanol at ambient temperature for two days, an addition product (**24**) was obtained in 38% yield instead of a condensation product (62JCS2222).

Both amino groups of 3,5-diamino-4-phenylpyrazole reacted with EMME during 2 min. at reflux [83JCS(P1)11]. The amino group at position 3 underwent a cyclocondensation reaction to form the bicyclic pyrazolo[1,5-*a*]pyrimidine, while the amino group at position 5 participated in an addition reaction to give a (2,2-diethoxycarbonyl-1-ethoxyethyl)amino side-chain. Pyrazolo[1,5-*a*]pyridine (**25**) was obtained in 27% yield.

Reaction conditions mainly depend on the reactivity and solubility of the amines. Reactions can be carried out in the presence or absence of a solvent (e.g., 39JA2890; 46JA1264, 46JA1268, 46JA1277; 47JA374) at room temperature (e.g., 46JA1277; 48USP2449226; 49BRP62797, 49JCS1017) or at elevated temperature, sometimes under an inert atmosphere (e.g., 46JA1204). In certain cases, the alcohol formed is distilled off (e.g., 46JA1204, 46JA1264, 46JA1277) or the reaction is carried out under reduced pressure (e.g., 46JA1204, 46JA1327; 49BRP627297, 49JCS1017).

As solvent, alcohols [e.g., 39JA2890; 66JMC774; 69GEP1908542; 75JCS(P1)1910], water (e.g., 86MI9; 87MI4), aqueous ethanol (e.g., 69JA6683), dioxane (e.g., 51JA1844; 82HCA2465; 86T3537), diethyl ether (e.g., 88EUP269295), methylene chloride (e.g., 48JA4063), hexane (e.g., 62JOC306), ethyl acetate (e.g., 74NEP11324), benzene (e.g., 51JOC1414; 56JCS3079), nitrobenzene (e.g., 54JA2429), toluene (e.g., 69GEP1908262; 87JHC1509), xylene (e.g., 58JCS828; 59MI2; 87JHC215), triethylamine



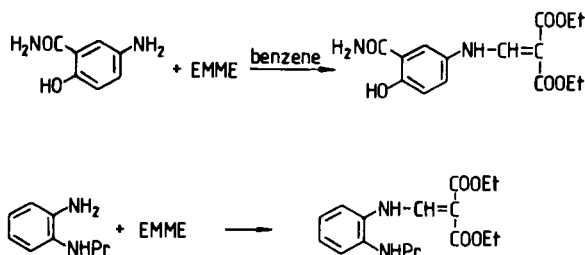
SCHEME 7

79LA950], other dialkyl ethoxymethylenemalonates (e.g., 74MIP1; 76ACH91; 86GEP3519926), ethyl methyl ethoxymethylenemalonate [e.g., 75JCS(P1)1517], dibenzyl ethoxymethylenemalonate (e.g., 74MIP1; 76ACH91), di-(4-methoxybenzyl) (4-methoxybenzyloxy)methylenemalonate (e.g., 86EUP218423), di-(2-acetoxyethyl) ethoxymethylenemalonate (e.g., 85BEP902586), dimethyl 1-ethoxyethylidenemalonate (e.g., 69JA6683), diethyl (ethylthio)methylenemalonate (e.g., 52LA48) are also sometimes used (Scheme 7).

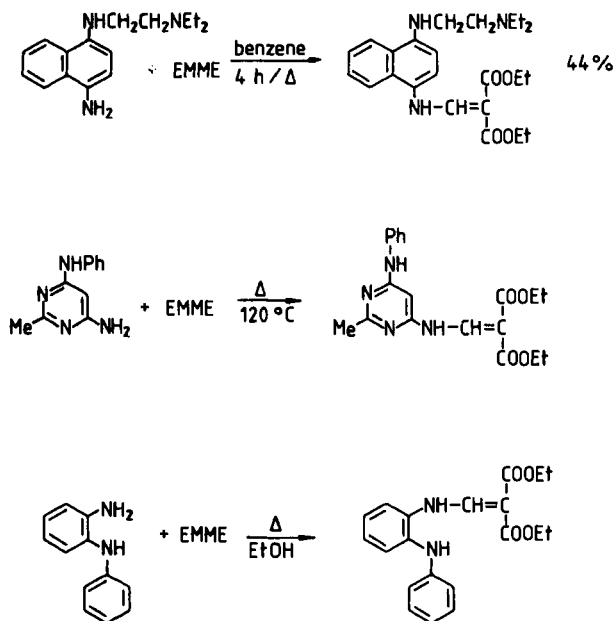
Aliphatic amines proved to be more reactive than aromatic amines with EMME [e.g., 76JCS(P1)1331]. Aromatic amines react more easily than the amino portion of the carboxamido group (e.g., 75IJC1275) (Scheme 8).

The primary amino group reacts much faster than the secondary amino group (e.g., 64JMC68, 64JMC487; 70CPB1385; 77GEP2612314; 78GEP2737542). Both 2-nitroaniline and *N*-methylaniline react less readily than aniline with EMME, but if these two groups are present at the same time (*N*-methyl-2-nitroaniline was used), no reaction occurred at all (59JCS2401) (Scheme 9).

Condensations of secondary amines with EMME generally require a higher temperature and a longer reaction time than those of primary amines (e.g., 71JHC357; 72HCA1319; 74JMC137). The hydrazino group reacted more easily than the amino group with EMME (70CPB1385) (Scheme 10).



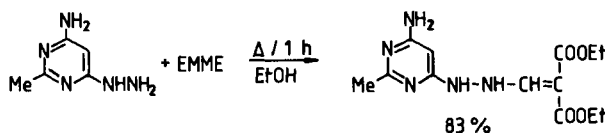
SCHEME 8



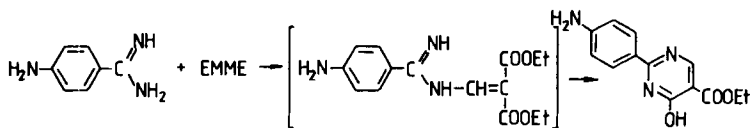
SCHEME 9

The amidine group reacted more easily than the aromatic amino group with EMME in boiling ethanol; besides the condensation, ring closure usually takes place to give pyrimidinecarboxylate in good yield (e.g., 80EUP15772) (Scheme 11).

Chapter 7 (Section C) lists the amines that have been reacted with alkoxymethylenemalonates ($R^3 = H$). Aminomethylenemalonate (**13**) was prepared in 80% yield from diethyl (ethylthiomethylene)malonate with aqueous ammonium hydroxide at 0°C (52LA48).



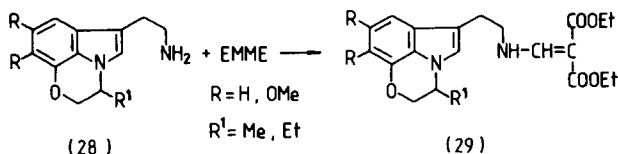
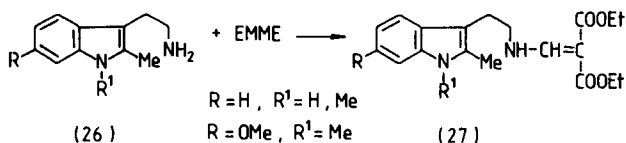
SCHEME 10



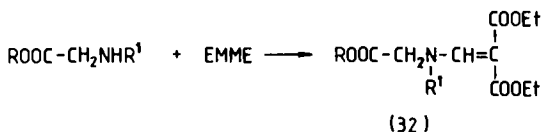
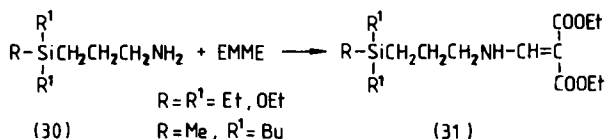
SCHEME 11

a. From Primary Amines

Tryptamine derivatives (**26**) were reacted with EMME to give *N*-[2-(3-indolyl)ethyl]aminomethylenemalonates (**27**) in nearly quantitative yields (77H1699; 79MI1).

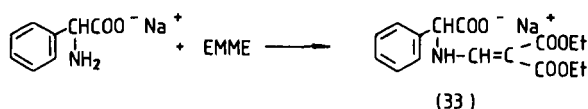


The reaction of additional tryptamine analogues (**28**) and EMME in boiling ethanol gave the appropriate aminomethylenemalonates (**29**) in 97–98% yields [85TL1769; 87JCS(P1)2079, 87T191].

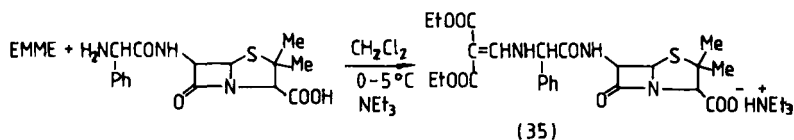
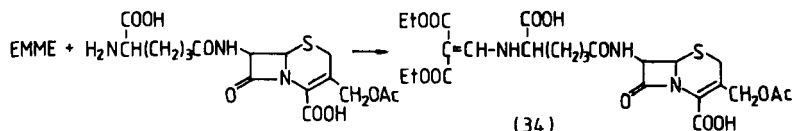


The reaction of propylamine derivatives (**30**) with EMME gave aminomethylenemalonates (**31**) in 80–84% yields (82MI7). Aminomethylenemalonates (**32**) were prepared in the exothermic reaction of glycine esters and EMME (77H1821).

The sodium salt of D-phenylglycine was reacted with EMME in boiling benzene for 3 hr, and the ethanol was then azeotropically removed to give the sodium salt of the aminomethylenemalonate (**33**) in 50% yield [80JAP(K)31040; 81CPB1998; 86MI2].



The mono- and disodium salts of Cephalosporin C were reacted with EMME in aqueous acetone at room temperature for 5–6 hr to give aminomethylenemalonate (**34**) (80GEP3002659; 82EUP45717).

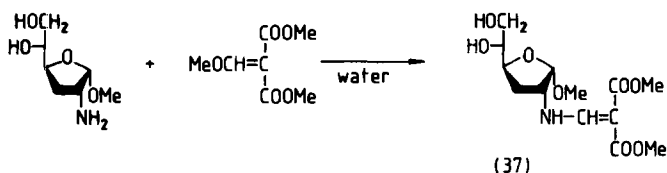


6-(D-2-Phenyl-2-aminoacetamido)penicillin-carboxylic acid was reacted with EMME in methylene chloride in the presence of triethylamine at 0–5°C to give the triethylammonium salt of 6-[D-2-phenyl-2-[(2,2-diethoxycarbonylvinylamino)-acetamido]} penicillincarboxylic acid (**35**) (74GEP2362978).

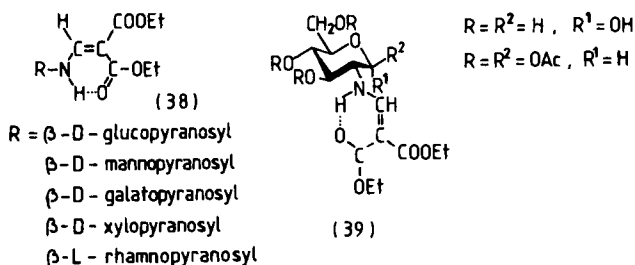
4-Amino-2,2,6,6-tetramethylpiperidine was reacted with EMME in ethanol at ambient temperature to yield (4-piperidinylamino)methylenemalonate (**36**) (77GEP2612314).



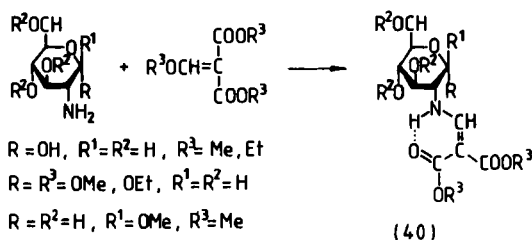
The reaction of methyl 2-amino-2-deoxy- α -D-glucofuranoside and dimethyl methoxymethylenemalonate in water for 5 h gave aminomethylenemalonate (37) in 92% yield (87MI4).



On reaction with EMME in methanol at ambient temperature, glycosylamines gave *N*-glycosylaminomethylenemalonates (38) in 8–44% yields (68MI1). Later, (β -D-glucopyranosylamino)methylenemalonate was prepared in 86% yield when the reaction was carried out in a 1:1 mixture of ethanol and methanol (86MI8). 2-Amino-2-deoxy- α -D-glucopyranose hydrochloride was reacted with EMME in the presence of triethylamine in boiling methanol and its anomeric β -D-*O*-acetyl derivative in dioxane to give the corresponding aminomethylenemalonate (39) in 82 and 58% yields, respectively (68MI1).

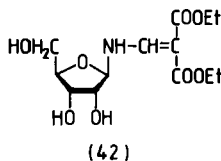
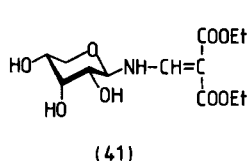


The hydrochlorides of 2-aminoglycoses were reacted with alkoxy-methylenemalonate in the presence of sodium carbonate in water at ambient temperature (method A) or in the presence of triethylamine in boiling ethanol for 0.5 hr (method B) to give aminomethylenemalonates (40). Method A afforded higher yields (97–98%) than method B (55–94%) (84MI7; 88MI4).

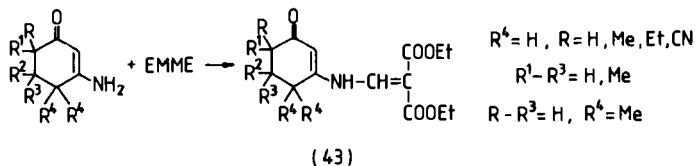


1-Amino-1-deoxy-D-fructose acetate was reacted with dimethyl methoxymethylenemalonate in the presence of sodium carbonate in water at ambient temperature for 4 hr to give aminomethylenemalonate (**19**) in 97% yield; several isomeric forms were present both in the solid state and in solution (86MI10) (see Table IV and Scheme 5B).

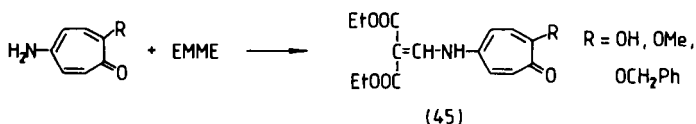
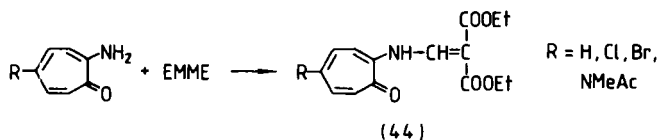
The reaction of D-ribosylamine and EMME in methanol at room temperature for 48 hr afforded a mixture of *N*-(β-D-ribofuranosyl)- and *N*-(β-D-ribofuranosyl)aminomethylenemalonates (**41** and **42**) in 48 and 8% yields, respectively (88M11).



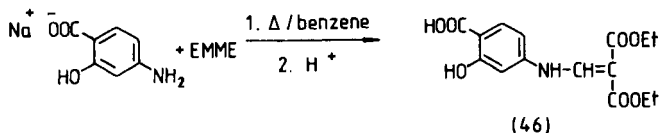
The reaction of 1-amino-1-cyclohexen-3-ones with EMME in the presence of *p*-toluenesulfonic acid at 120–135°C for 2–18 hr gave *N*-cyclohexenylaminomethylenemalonates (**43**) in 71–93% yields [75JHC 1245; 79JAP(K)119484; 80GEP2947948, 80GEP3008884; 82JHC289]. When 1-amino-1-cyclohexen-3-ones were reacted with EMME in benzene at 55–60°C for 1.5–2.0 hr 1-cyclohexenylaminomethylenemalonates (**43**) were obtained in only moderate yields [82JAP(K)116048].



2-Amino- and 5-amino-2,4,6-cycloheptatrien-1-ones were reacted with EMME at 140°C for 1.5–2.0 hr to afford (1-oxocycloheptatrien-2- and 5-ylamino)methylenemalonates (**44** and **45**) in good yields (83USP4381304, 83USP4382088).

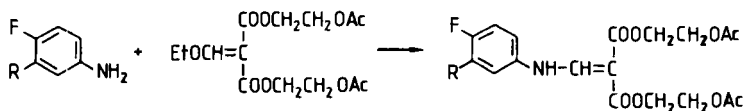
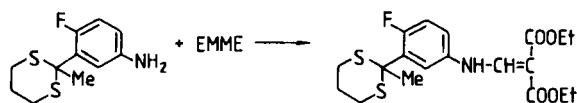


5-Aminosalicylamide reacted readily with EMME in boiling benzene for 4 hr to give aminomethylenemalonate in 75% yield, but the reactions of 4-aminosalicylamide and 4-aminosalicylic acid with EMME in boiling benzene or xylene for 4–24 hr were unsuccessful (75IJC1275). However, if the sodium salt of 4-aminosalicylic acid was reacted under similar conditions, the required aminomethylenemalonate (46) was obtained.



4-Fluoro-3-(2-methyl-1,3-dithian-2-yl)aniline was reacted successfully with EMME in toluene. Toluene was distilled off until the head temperature reached 120–125°C (84EUP106489; 85EUP153163; 87JHC1509).

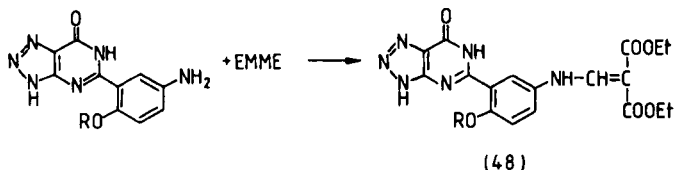
Di-(2-acetoxyethyl) *N*-(4-fluorophenyl)aminomethylenemalonates (47) were prepared in the reaction of 3-substituted 4-fluoroaniline and di-(2-acetoxyethyl) ethoxymethylenemalonate in the presence of Triton B under



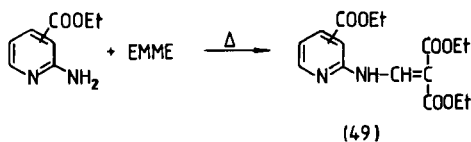
(47)

reflux for 8 hr or in boiling benzene in the presence of Triton B for 30 min (85BEP902586).

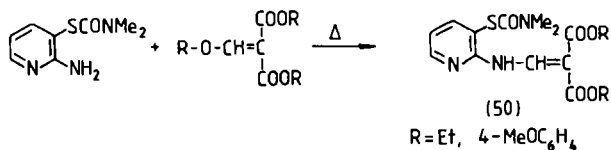
3-Aminobenzenesulfonic acid and 3-aminobenzenesulfonyl chloride failed to react with EMME (77JMC1001). (Substituted phenylamino)methylenemalonates (**48**) were prepared in the reaction of 2-(5-amino-2-alkoxyphenyl)-8-azapurin-6-ones and EMME at 140°C (78GEP2747199; 82SZP627755).



Ethyl 2-aminopyridinecarboxylates reacted smoothly with EMME at 120–130°C in 30 min, except the 3-carboxylate, which was reacted at 150–170°C to give the corresponding 2-pyridylaminomethylenemalonate (**49**) in 78–92% yields (78MI5).

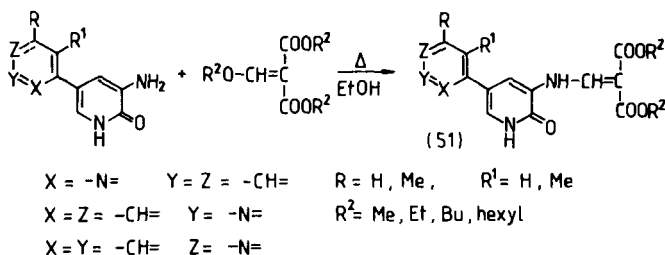


2-Amino-3-(*N,N*-dimethylcarbamoyl)thiopyridine was reacted with EMME or di-(4-methoxybenzyl) (4-methoxybenzyloxy)methylenemalonate at 100–120°C for 1 hr to afford 2-pyridylaminomethylenemalonates (**50**) in 76 and 80% yields, respectively (86EUP218423).

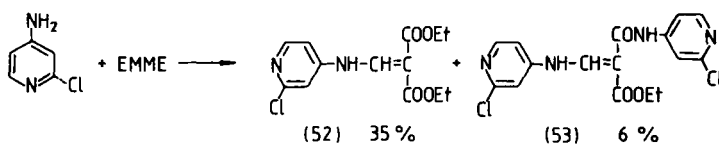


The condensation of 2-amino-6-methylpyridine and EMME was carried out in methyl-phenyl-polysiloxanes at 90–100°C to give high-purity (99%) diethyl *N*-(6-methyl-2-pyridyl)aminomethylenemalonate in 97% yield (84GEP3308089). 3-Amino-5-(pyridyl)-2-(1*H*)-pyridones were reacted with dialkyl alkoxy methylenemalonates in boiling ethanol for 6.0–6.5 h to

give 3-pyridylaminomethylenemalonates (**51**) in good yields (78USP41 07315; 79USP4137233; 81CP1103253).



After the reaction mixture of 4-amino-2-chloropyridine and EMME had been heated at 90°C for 10 hr, not only 4-pyridylaminomethylenemalonate (**52**), but also a malonamate derivative (**53**) was isolated (82CPB2399).



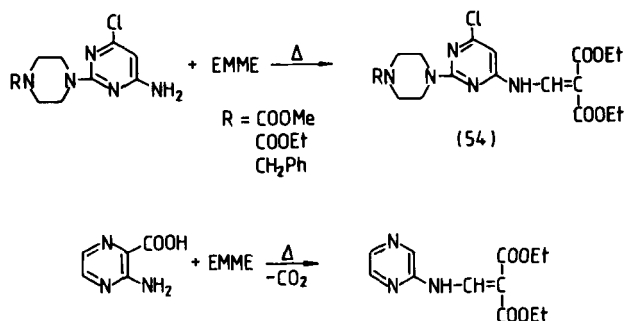
It was initially reported that 2-aminopyrimidine failed to react with EMME (58M12), but one year later it was found that when the reaction was carried out in diphenyl ether upon heating for 0.5–4 hr, 2-pyrimidinylaminomethylenemalonate could be obtained in 80% yield (59M13). 2-Pyrimidinylaminomethylenemalonate was also prepared in 59% yield in the reaction of 2-aminopyrimidine and EMME at 135°C for 1 hr (72JMC1203) (Scheme 12).

4-Amino-6-chloro-2-(1-piperazinyl)pyrimidines were reacted with EMME at 140–150°C for 9–10 hr to give 4-pyrimidinylaminomethylenemalonates (**54**) in 77.2–79.0% yields [87JAP(K)142177].

The reaction of 3-aminopyrazine-2-carboxylic acid and EMME at 160–180°C for 2 hr, or in diphenyl ether at 200°C for 2 hr, afforded 2-pyrazinylaminomethylenemalonate in 60% yield (70T3069; 71IJC201) (Scheme 13).

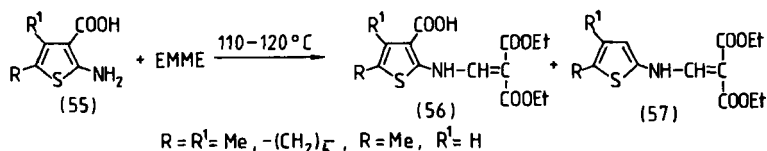


SCHEME 12

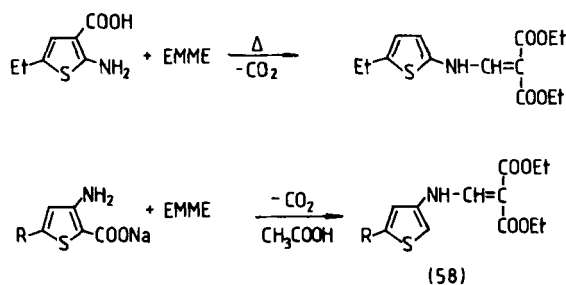


SCHEME 13

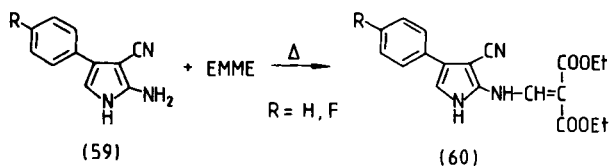
The reaction of 2-aminothiophene-3-carboxylic acids (**55**) or 2-aminotetrahydrobenzo(*b*)thiophene-3-carboxylic acid [**55**, $\text{R} = \text{R}^1 = -(\text{CH}_2)_4-$] and EMME by heating at 110 – 120°C for 1–2 hr gave a mixture of 3-carboxylic acids (**56**) and decarboxylated derivatives (**57**) (75GEP2435025).



2-Amino-5-ethylthiophene-3-carboxylic acid was reacted with EMME in boiling toluene under nitrogen for 6 hr to afford *N*-(5-ethyl-2-thienyl)aminomethylenemalonate in 59% yield (84EUP126970). The reactions of bis(2- and 3-thienylammonium) hexachlorostannates and EMME, involving heating in pyridine at 40 – 50°C over a period of 24 hr, gave 2- and 3-thienylaminomethylenemalonates (**57**, $\text{R} = \text{R}^1 = \text{H}$ and **58**, $\text{R} = \text{H}$) in 80 and 70% yields, respectively (77JHC807). Similar reactions did not occur in ethanol.

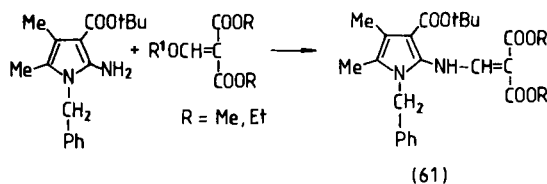


Sodium 3-aminothiophene-2-carboxylates were reacted with EMME in boiling toluene in the presence of acetic acid for 4–6 hr to give 3-thienylaminomethylenemalonates (**58**) in moderate yields (87T3295; 88EUP269295). The 5-bromo derivative of compound **58** ($R = \text{Br}$) was prepared in the reaction of 3-amino-5-bromothiophene and EMME, but 2-amino-5-nitrothiophene failed to react (87T3295).

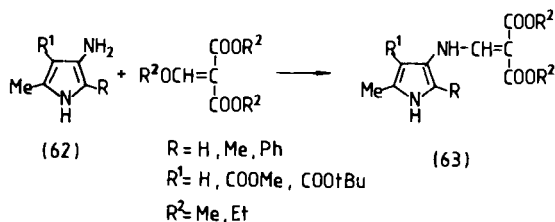


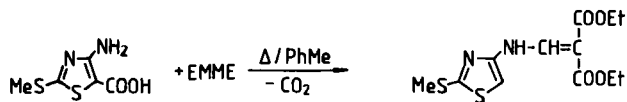
The reactions of 2-aminopyrroles (**59**) and EMME in ethanol at room temperature for 20–24 hr or at reflux temperature for 30 min gave 2-pyrrolylaminoethylenemalonates (**60**) in 60–74% yields (86SAP9289; 87FES787, 87JHC297).

tert-Butyl 2-amino-1-benzyl-4,5-dimethylpyrrole-3-carboxylate was reacted with dialkyl alkoxyethylenemalonates at 150–160°C for 2–3 hr to afford 2-pyrrolylaminoethylenemalonates (**61**) in 38–65% yields (85JHC1429).



The exothermic reactions of 3-aminopyrroles (**62**) and dialkyl alkoxyethylenemalonates in methanol or ethanol afforded 3-pyrrolylaminoethylenemalonates (**63**) in 67–85% yields (85JHC83, 85JHC729, 85JHC817).

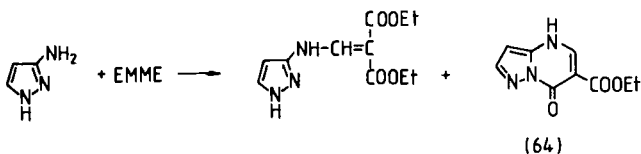




SCHEME 14

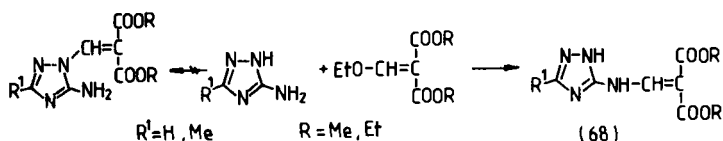
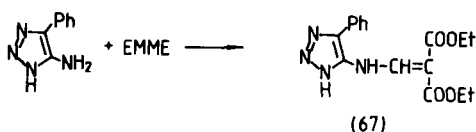
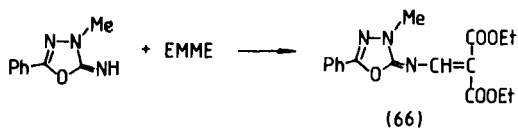
4-Amino-(2-methylthio)thiazole-5-carboxylic acid was reacted with EMME in boiling toluene for 2 hr to give *N*-(2-methylthiothiazol-4-yl)aminomethylenemalonate in 62% yield (84JHC1361) (Scheme 14).

The reaction of 3-aminopyrazole and EMME at 100°C for 30 min gave 10% of pyrazolo[1,5-*a*]pyrimidinecarboxylate (**64**) and 25% of 3-pyrazolylaminomethylenemalonate (70CB3252). When the reaction was carried out in boiling acetic acid for 3 hr, pyrazolo[1,5-*a*]pyrimidinecarboxylate (**64**) was isolated in 60% yield (62CPB620; 70CB3252). Heating of the reaction mixture of 5-substituted 2-amino-1,3,4-oxadiazoles and EMME at 130–140°C for 2–3 hr afforded *N*-(5-substituted 1,3,4-oxadiazol-2-yl)aminomethylenemalonates (**65**) in 40–92% yields [88IJC(B)293].



In the reaction of 5-phenyl-3-methyl-2-imino-1,3,4-oxadiazoline and EMME at 130°C for 30 min, *N*-(1,3,4-oxadiazolin-2-ylidene)aminomethylenemalonate (**66**) was obtained in 34% yield (70AP501). The reaction of 5-amino-4-phenyl-1,2,3-triazole and EMME in the presence of acetic acid in boiling benzene for 30 hr, or in boiling toluene for 3 hr, gave (1,2,3-triazol-5-ylamino)methylenemalonate (**67**) in 64–89% yields [71JCS(C)2156].

In patents, it was stated that one of the ring nitrogens of 3-amino-1,2,4-triazoles reacted with dialkyl ethoxymethylenemalonates in aqueous ethanol at room temperature (48USP2449226; 49USP2476549), but Williams later proved that the amino group was involved in these reactions and that (1,2,4-triazol-3-ylamino)methylenemalonates (**68**)

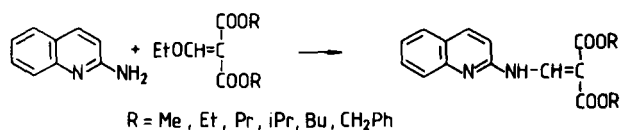


were the products (62JCS2222). Under similar conditions, diethyl 1-ethoxyethylidenemalonate did not react with 3-amino-1,2,4-triazole ($\text{R}^1 = \text{H}$) (62JCS2222).

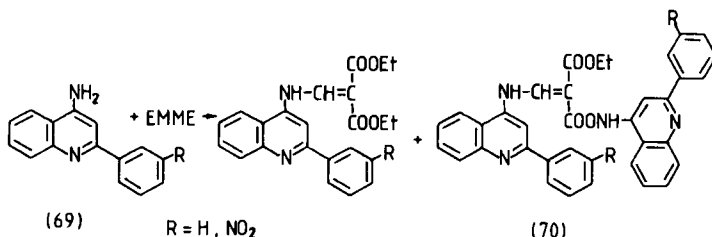
2-Quinolylaminomethylenemalonates were obtained in the reaction of 2-aminoquinoline and dialkyl ethoxymethylenemalonates by heating at 140–150°C for 1.5 hr (74MIP1) (Scheme 15).

4-Aminoquinolines (69) did not react with EMME in chloroform, but the reactions took place readily in refluxing xylene. At higher temperature, however, side-product (70) formation accompanied the condensation (58JCS828).

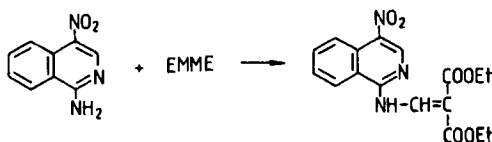
N-(4-Nitroisoquinolin-1-yl)aminomethylenemalonate was obtained in the reaction of 1-amino-4-nitroisoquinoline and EMME in the presence of sodium hydride in a mixture of dimethylformamide (DMF) and hexameth-



SCHEME 15

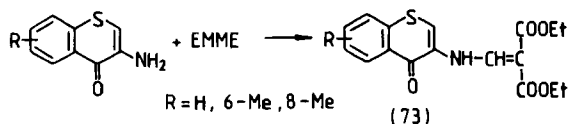
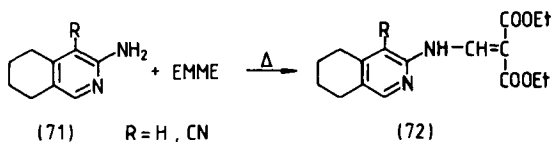


ylphosphortriamide at 5°C for 7 min (61% yield), or by heating in DMF at 150°C for 40 min (46% yield) [84JAP(K)172472] (Scheme 16).



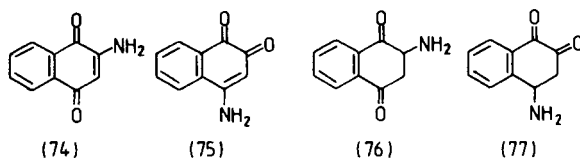
SCHEME 16

3-Amino-5,6,7,8-tetrahydroisoquinolines (**71**) were reacted with EMME at 150°C for 0.5–24 hr to give *N*-(tetrahydroisoquinolin-3-yl)aminomethylenemalonates in 82–87% yields (83KGS1279; 84KFZ931). 3-Benzothiopyranylaminomethylenemalonates (**73**) were prepared in 78–88% yields in the reactions of 3-aminothiochromones and EMME at 140°C for 5 hr under nitrogen (85JHC89).

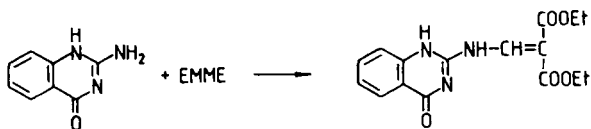
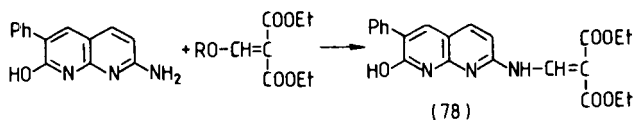


2-Amino-1,4- and 4-amino-1,2-naphthoquinones (**74** and **75**) failed to react with EMME, probably because of the “amide-like” character of the amino group. However, their 2,3- and 3,4-dihydro derivatives (**76** and **77**)

readily reacted with EMME to give the corresponding aminomethylenemalonates (67JOC3210).



2-Amino-6-phenyl-7-hydroxy-1,8-naphthyridine reacted with an excess of diethyl alkoxymethylenemalonates in the presence of concentrated hydrochloric acid or in acetic acid to afford *N*-(1,8-naphthyridin-2-yl)aminomethylenemalonate (**78**) in 44–63% yields (69G677).



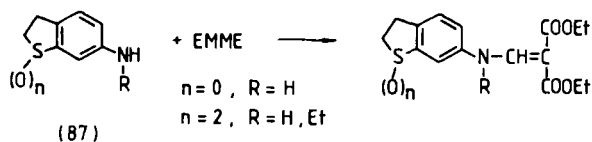
The condensation of 2-amino-1,4-dihydro-4-quinazolinone and EMME at 180°C for 1 hr afforded *N*-(4-oxo-1,4-dihydro-2-quinazolyl)aminomethylenemalonate in 90% yield (89JHC161).

N-(1,4-Benzoxazin-6- and -7-yl)aminomethylenemalonates (**80** and **82**) were prepared in 76–91% yields when 6- and 7-amino-1,4-benzoxazines (**79** and **80**) were reacted with EMME by heating on a steam-bath for 2 hr [88IJC(B)649].

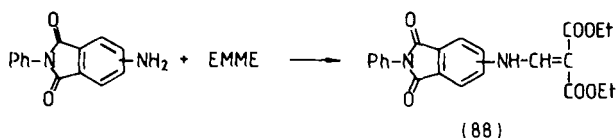
5-, 6-, 7-, and 8-Amino-1,4-benzothiazines (**83**) were reacted with EMME at 100–120°C for 60–90 min to give 1,4-benzothiazinylaminomethylenemalonates (**84**) in 24–91% yields (84MI6).

The reaction of 1-amino-5-benzyl-5,8-dihydropyrido[4,3-*d*]pyrimidin-8-one and EMME in boiling DMF for 4 hr gave *N*-(pyridopyrimidin-1-yl)aminomethylenemalonate (**85**) in 48% yield (84KGS532).

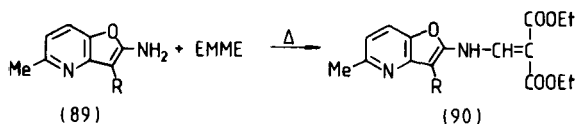
6-Aminobenzo[*b*]thiophenes (**87**) were reacted with EMME at 110–140°C to give *N*-[benzo[*b*]thien-6-yl]aminomethylenemalonates in 91–93% yields (88AP241).



4- and 5-Amino-2-phenyl-1,3,-dioxoisindoles were reacted with EMME to afford *N*-(2-phenyl-1,3-dioxoisindolyl)aminomethylenemalonates (**88**) (87MI1).



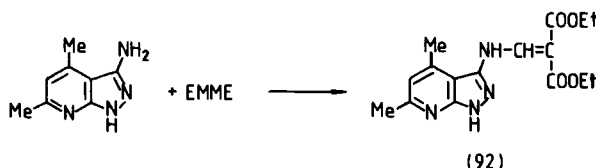
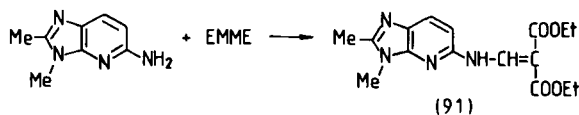
2-Aminofuro[3,2-*b*]pyridines (**89**) were reacted with EMME at 130°C for 2.5 hr to afford *N*-(furopyridin-2-yl)aminomethylenemalonates (**90**) in 10–47% yields (84G211). In the case of 3-carboxamide (**89**, $R = CONH_2$), no reaction took place.



The reaction of 5-aminobenzimidazole and EMME in boiling ethanol for 2 hr gave 5-benzimidazolylaminomethylenemalonate in 83% yield (86EUP187705). Similarly aminomethylenemalonates were prepared from 4- and 5-aminobenzimidazoles and -benzotriazoles (82MI1; 88MI11, 88MI13; 89CCC713, 89FES609, 89FES619).

Diethyl *N*-(2-methyl-2*H*-benzotriazol-5-yl)-aminomethylenemalonate was prepared by both Sanna and Paglietti (89FES609) and Milata *et al.* (89CCC713), but for characterization of the product, they gave different melting points (102–104°C vs. 89–91°C).

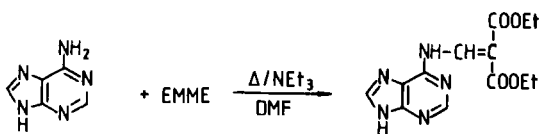
5-Amino-2,3-dimethyl-3*H*-imidazo[4,5-*b*]pyridine was reacted with EMME in boiling toluene for 2 hr to afford *N*-(imidazopyridin-5-yl)aminomethylenemalonate (**91**) in 84% yield (86EUP174832). The reaction of 3-amino-4,6-dimethyl-1*H*-pyrazolo[3,4-*b*]pyridine and EMME yielded *N*-(4,6-dimethyl-1*H*-pyrazolo[3,4-*b*]pyridin-3-yl)aminomethylenemalonate (**92**) (87MI5).



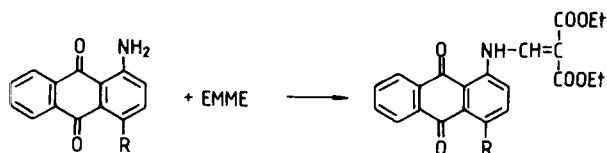
In the reaction of adenine and EMME in the presence of triethylamine in boiling dimethylformamide for 16 hr, 6-purinyllaminomethylenemalonate was obtained in 75% yield (86EUP174832) (Scheme 17).

Sivasankaran *et al.* condensed 1-amino-, 1-amino-4-methoxy-, 1-amino-4-hydroxy-, and 2-aminoanthraquinones with EMME in boiling xylene for 4 hr, and obtained anthraquinolylaminomethylenemalonates in 92%, 83%, 78%, and 56% yields, respectively (59MI2). Ayyangaar *et al.* prepared the 1-anthraquinolylaminomethylenemalonate in 99% yield when 1-aminoanthraquinone was reacted with EMME in the presence of an excess of aluminum chloride at 30°C for 1 h (87MI8) (Scheme 18).

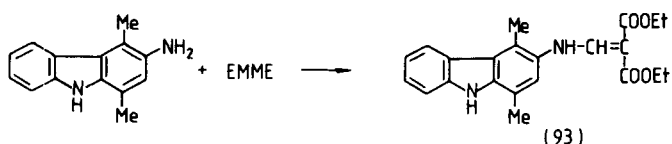
3-Amino-1,4-dimethylcarbazole was reacted with EMME to give 3-carbazolylaminomethylenemalonate (**93**) (87CPB425). Mixtures of tricyclic amino derivatives (**94**, X = CH₂, S, N(CH₂)₂NMe₂) and EMME were



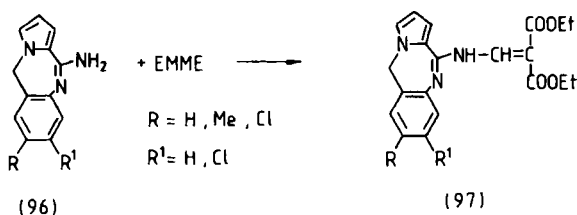
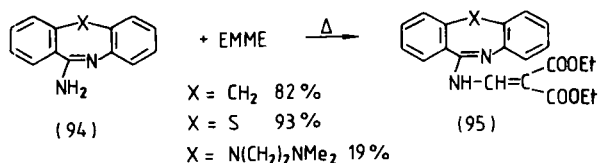
SCHEME 17



SCHEME 18

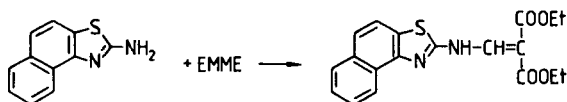
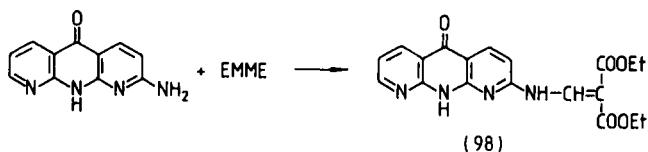


heated under nitrogen at 100°C for 2 hr to give aminomethylenemalonates (95) in 19–93% yields (80JHC341).

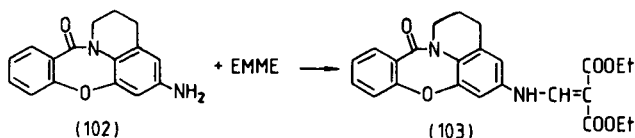
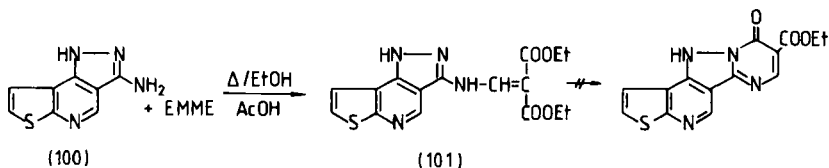
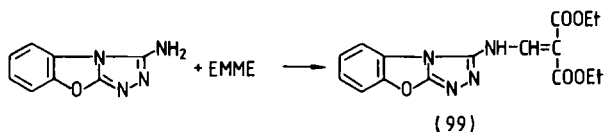


N-(5*H*-Pyrrolo[2,1-*c*]-1,4-benzodiazepin-11-yl)-aminomethylene-malonates (97) were obtained in 57–88% yields in the reactions of 11-amino-5*H*-pyrrolo[2,1-*c*]-1,4-benzodiazepines (96) and EMME at 100°C for 30 min (85CP1197242, 85JHC305).

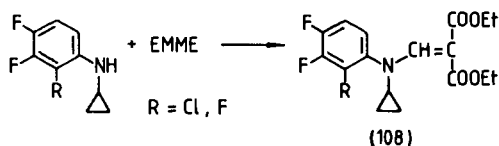
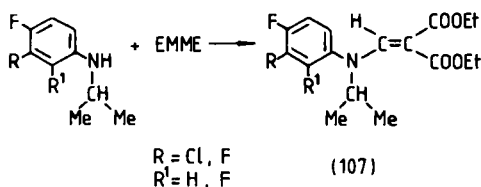
2-Aminoanthryridin-5(10*H*)-one was reacted with EMME at reflux temperature for 1 hr to yield 2-anthryridinylaminomethylenemalonate (98) in 82% yield (74FES366). The condensation of 2-aminonaphiho[1,2-*d*]thiazole with EMME at 125°C for 20 min afforded *N*-(naphiho[1,2-*d*]thiazol-2-yl)aminomethylenemalonate in 95% yield (85AP84).



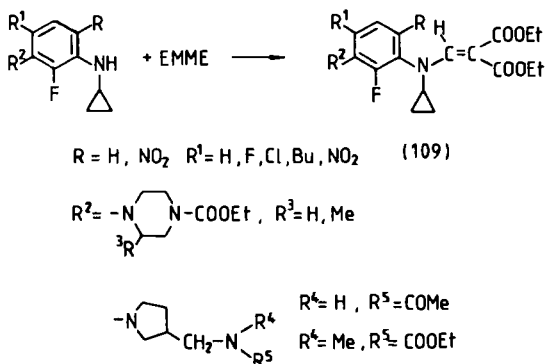
The reaction of 3-amino-1,2,4-triazolo[3,4-*b*]benzoxazole and EMME in boiling ethanol for 2 hr gave condensation product **99** in 84% yield (89H925). 3-Amino-1*H*-pyrazolo[3,4-*d*]thieno[2,3-*b*]pyridine (**100**) was reacted with EMME in boiling ethanol for 1.5 hr to give *N*-(pyrazolothienopyridin-3-yl)aminomethylenemalonate (**101**) in 50% yield. When the amine (**100**) and EMME were reacted in boiling acetic acid for 14 hr, instead of the expected cyclocondensation, only condensation occurred to give the aminomethylenemalonate (**101**) (83M1079).

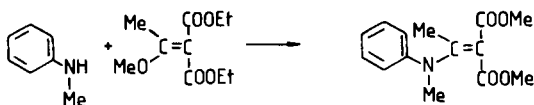


The reactions of *N*-isopropylanilines and EMME at 160–170°C for 1–3 hr gave *N*-isopropyl-*N*-phenyl-aminomethylenemalonates (**107**) in 52–99% yields [85GEP3433924, 85JAP(K)28964, 85JAP(K)126271]. *N*-Cyclopropyl-*N*-(2,3,4-trihalophenyl)aminomethylenemalonates (**108**) were obtained in the reactions of anilines and EMME at 100–135°C for 10.5 hr ($R = \text{Cl}$ (85SAP3954; 86EUP183129, 86EUP195316) or at 150–160°C for 1.5 hr ($R = \text{F}$ (84BEP899399).



N-Cyclopropylanilines were reacted with EMME at 140–170°C for 2–25 hr to afford *N*-cyclopropyl-*N*-arylaminoethylenemalonates (**109**) in 68–72% yields [86JAP(K)143363, 86JAP(K)143364; 87JAP(K)26272,

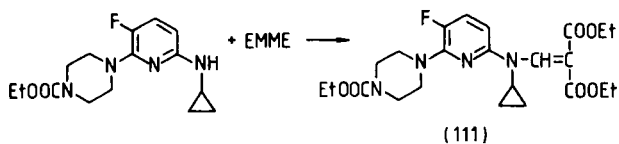
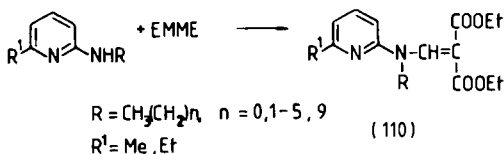




SCHEME 20

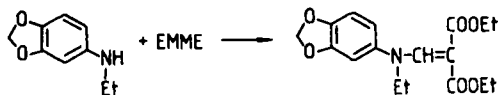
87NEP471; 88EUP287951]. *N*-Methylaniline was reacted with dimethyl 1-methoxyethylidenemalonate at 180°C for 1.5 hr to give dimethyl 1-(*N*-methyl-*N*-phenylamino)ethylidenemalonate in 32% yield (69JA6683) (Scheme 20).

2-(Substituted amino)-6-alkylpyridines were reacted with EMME at 100–110°C for 8–12 hr to give *N*-substituted *N*-(2-pyridyl)aminomethylenemalonates (**110**) (71GEP2108046; 72JAP25349). 2-(Cyclopropylamino)-6-(4-ethoxycarbonylpiperazino)-5-fluoropyridine was reacted in boiling xylene for 24 hr to afford the corresponding 2-pyridylaminomethylenemalonate (**111**) in 39% yield (85EUP153163, 85EUP153828, 85EUP159174; 86EUP172651; 88EUP265230).



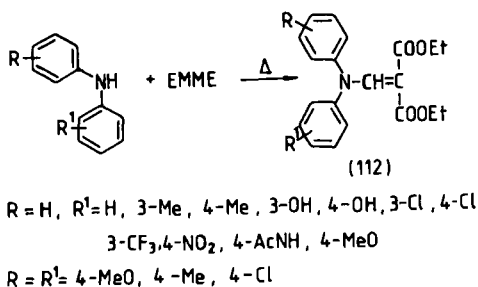
3-Methylamino-6-morpholinopyridazine was reacted with EMME at 120°C for 2–3 hr to afford diethyl *N*-methyl-*N*-(6-morpholino-3-pyridazinyl)-aminomethylenemalonate in 54% yield (88JHC1535).

N-Ethyl-3,4-methylenedioxyaniline was reacted with EMME in boiling dioxane for 6 hr, in the presence of two drops of a solution of 40% Triton B in methanol, to give *N*-ethyl-*N*-(3,4-methylenedioxyphenyl)aminomethylenemalonate in 87% yield [71JAP34707; 72JCS(P1)173]. No reaction occurred in the absence of the Triton B catalyst [72JCS(P1)173] (Scheme 21).

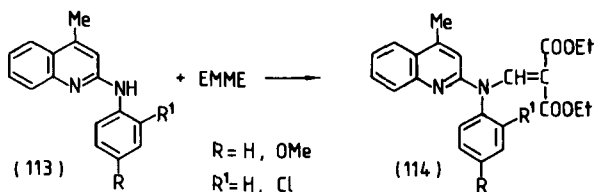


SCHEME 21

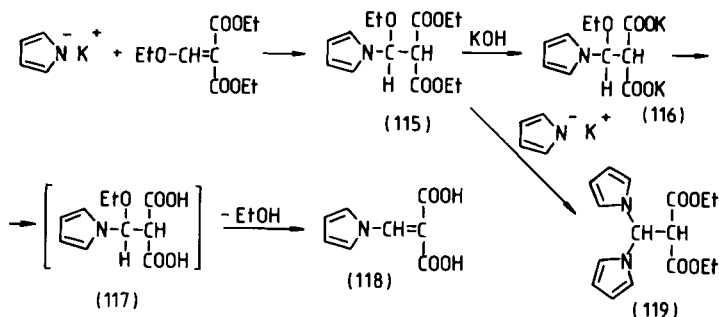
The reaction of *N*-(2,2,2-trifluoroethyl)-3,4-methylenedioxyaniline and EMME at 140–150°C for 3 hr gave diethyl *N*-(2,2,2-trifluoroethyl)-*N*-(3,4-methylenedioxyphenyl)aminomethylenemalonate (76GEP2534869). *N,N*-Diphenylaminomethylenemalonates (**112**) were prepared from the reactions of diphenylamines and EMME at 190–210°C for 0.75–2.0 hr (69BRP1147336).



2-Anilinoquinolines (**113**) were reacted with EMME to give *N*-(2-quinoliny)-*N*-phenylaminomethylenemalonates (**114**) (87JIC481).



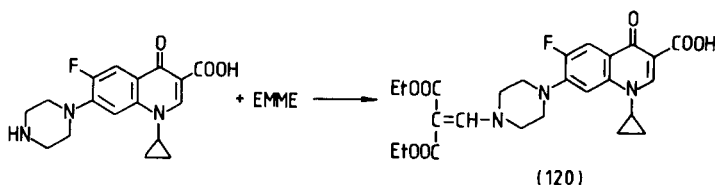
In the reaction of EMME and the potassium salt of pyrrole in tetrahydrofuran (THF) at 0°C for 30 min, an addition product, ethoxy(1-pyrrolyl)methylmalonate (**115**), could be isolated in 85% yield (82CB714). This ester (**115**) was hydrolyzed with potassium hydroxide in aqueous ethanol at reflux temperature to yield 95% dipotassium ethoxy(1-pyrrolyl)methylenemalonate (**116**), from which 1-pyrrolylmethylenemalonic acid (**118**) was



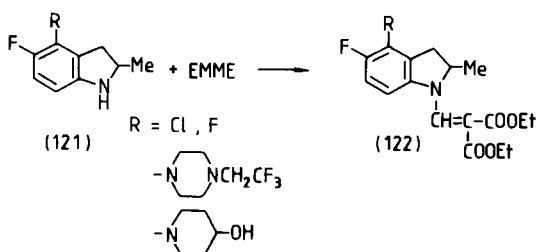
SCHEME 22

obtained in 67% yield by acidification with hydrochloric acid via ethoxy(1-pyrrolyl)methylmalonic acid (117). The reaction of diethyl ethoxy(1-pyrrolyl)methylmalonate (115) and the potassium salt of pyrrole in THF gave dipyrrolylmethylmalonate (119) in 57% yield (Scheme 22).

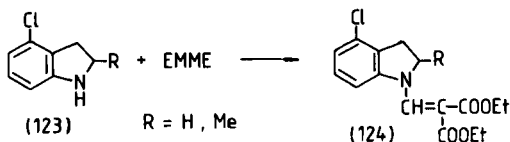
Ciprofloxacin was reacted with EMME in aqueous dioxane in the presence of sodium hydroxide at ambient temperature for 5 hr to give aminomethylenemalonate (120) in 48% yield (84GEP3306772, 84GEP3308908).



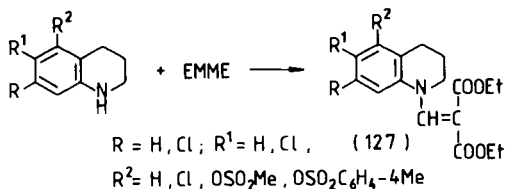
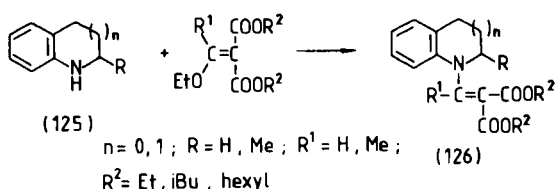
Indolines (121) were reacted with EMME at 140–160°C for 0.5 hr to afford 1-indolinylmethylenemalonates (122) [83JAP(K)13585, 83JAP(K)90511]. Indolines (123) were condensed with EMME at



110–120°C to give 1-indolylmethylenemalonates (**124**) (79GEP2914218, 79GEP2914258). Similarly, other 1-indolylmethylenemalonates were prepared (82BEP891046, 82BEP891537).

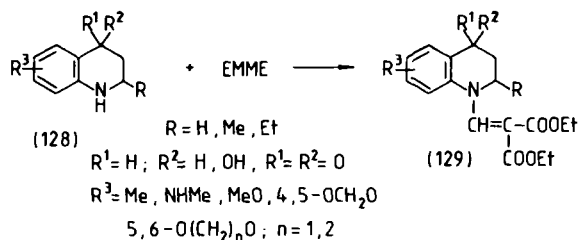


Indolines and tetrahydroquinolines (**125**, $n = 0, 1$) were reacted with dialkyl ethoxymethylenemalonates at 150°C for 5 hr, and the alcohol formed was distilled off to give condensation products (**126**, $n = 0, 1$) in 80–95% yields (86GEP3519926).

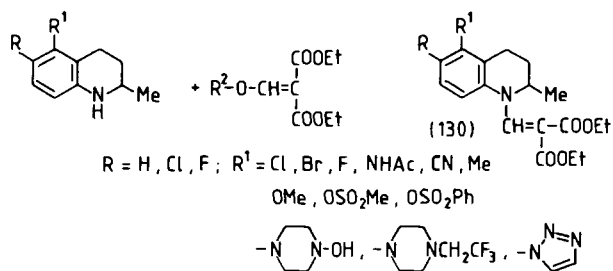


((Tetrahydroquinolin-1-yl)methylenemalonates (**127**) were prepared in the reactions of tetrahydroquinolines and EMME at 110–120°C [79GEP2914218, 79GEP2914258; 80JAP(K)38364]. Tetrahydroquinolines (**128**) were reacted with EMME at 120–180°C for 1–3 hr to give (tetrahydroquinolin-1-yl)methylenemalonates (**129**) (73GEP2264163; 74GEP-2415763; 76MIP3, 76USP3969463, 76USP3976651, 76USP3985753, 76USP3985882; 77USP4001243, 77USP4014877).

Tetrahydroquinaldines were reacted with alkoxymethylenemalonates at 120–160°C for 0.5–5 hr [81FRP2463771, 81FRP2476079; 81JAP(K)55388, 81JAP(K)59773; 82BEP891046, 82BEP891537; 83EUP79162, 83JAP(K)2-



9789, 83JAP(K)90511, 83USP4380543, 83USP4404207, 83USP4416884; 84EUP109284, 84EUP109285, 84EUP119779, 84NEP1115; 85USP4524-148; 87EUP245913; 89MI2] or in boiling xylene for 24–28 hr (83EUP79-162, 83USP4380543; 84NEP1115, 84USP4443447; 86USP4565872) to afford (2-methyltetrahydroquinolin-1-yl)methylenemalonates (130).



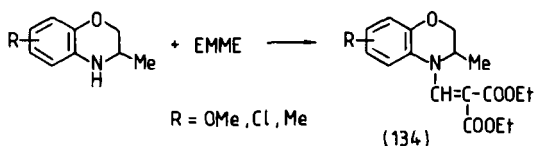
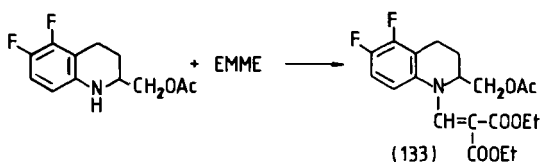
The optically active (2,5-dimethyl-6-fluorotetrahydroquinolin-1-yl)-methylenemalonates (131) were prepared in the reactions of optically active enantiomers of 2,5-dimethyl-6-fluorotetrahydroquinoline and EMME at 135–140°C for 1 hr (87JMC839). In a similar way, the 2-desmethyl derivative of 131 was prepared.

4-Oxotetrahydroquinolines were reacted with EMME at 200–210°C for 1.5 hr to give (4-oxotetrahydroquinolin-1-yl)methylenemalonates (132) in nearly quantitative yields (86EUP203795).

2-Acetoxyethyl-5,6-difluorotetrahydroquinoline was reacted with

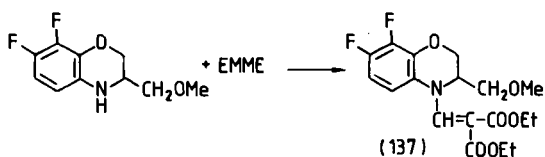
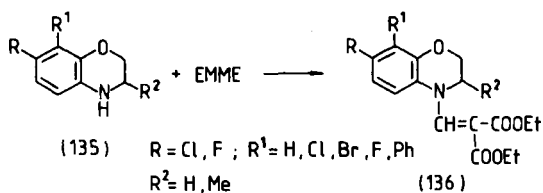


EMME at 140°C for 8 hr to yield (tetrahydroquinolin-1-yl)methylenemalonate **(133)** (84EUP101829).



Dihydro-1,4-benzoxazines were reacted with EMME at 110–120°C for 3 hr to give 4-benzoxazinylmethylenemalonates **(134)** (75USP3883522).

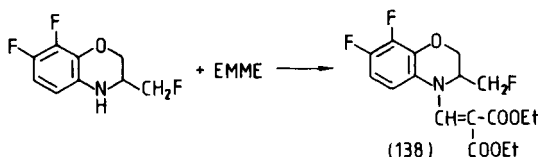
Racemic or optically active ($R^2 \neq H$) or ^{14}C -labeled ($R = F$, $R^1 = H$, $R^2 = Me$) 1,4-benzoxazines **(135)** were reacted with EMME at 130–140°C for 1–5 hr to give (1,4-benzoxazin-4-yl)methylenemalonates **(136)** in good



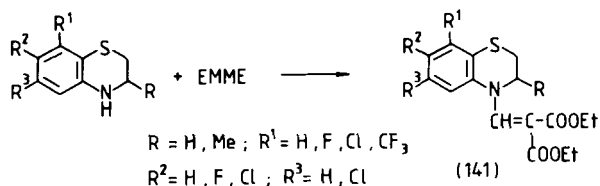
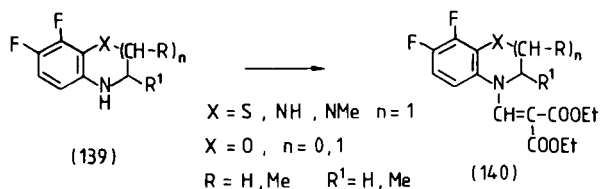
yields [83JAP(K)52290; 84CPB4907, 84JAP(K)122493, 84USP4443447; 85JAP(K)126290; 86EUP184384, 86EUP206283, 86MI14].

3-Methoxymethyl-7,8-difluorodihydro-1,4-benzoxazine was reacted with EMME at 105–115°C for 2 hr to afford (1,4-benzoxazin-4-yl)methylenemalonate (**137**) in 76% yield (84EUP101829).

(1,4-Benzoxazin-4-yl)methylenemalonate (**138**) was obtained in the reaction of 7,8-difluoro-3-fluoromethyl-1,4-benzoxazine and EMME at 130–140°C for 3 hr [86JAP(K)204188].



Bicyclic heterocycles (**139**) were reacted with EMME at 130–150°C for 1.5–5.0 hr to give condensation products (**140**) in good yields [82JAP(K)-203085].

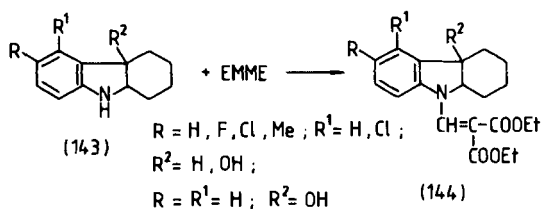


Tetrahydro-1,4-benzothiazines were condensed with EMME at 120°C for 1.75–2 hr to give (1,4-benzothiazin-4-yl)methylenemalonates (**141**) [85JAP(K)208987; 87JMC465].

Hexahydro-3-benzazocine was reacted with EMME in boiling ethanol for 1 hr to give the 3-benzazocinylmethylenemalonate (**142**) in 95% yield (74USP3840522).

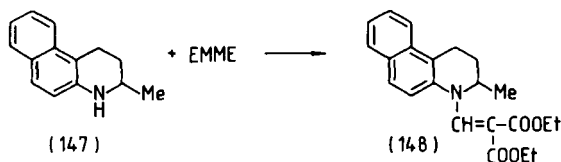
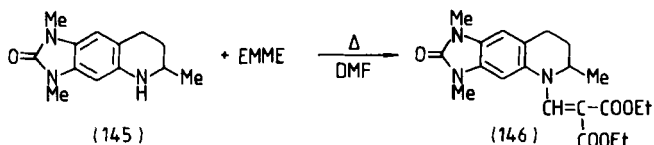


The reactions of hexahydrocarbazoles (**143**, $R^2 = H$) and EMME at 110°C for 30 min afforded 9-carbazolylmethylenemalonates (**144**, $R^2 = H$) in good yields (79GEP2849158, 79GEP2914218, 79GEP2914258).



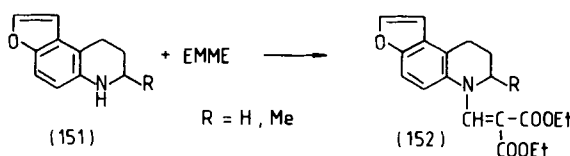
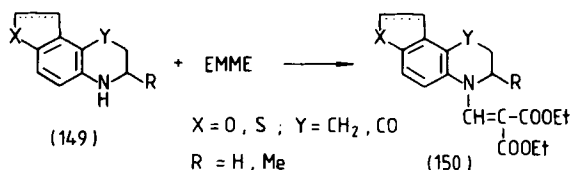
The reaction of 4a-hydroxy-1,2,3,4,4a,9a-hexahydrocarbazole (**143**, $R = R^1 = H, R^2 = OH$) and EMME gave 9-carbazolylmethylenemalonate (**144**, $R = R^1 = H, R^2 = OH$), which was dehydrated to the corresponding diethyl (1,2,3,4-tetrahydrocarbazol-9-yl)methylenemalonate in methanol in the presence of picric acid (60JA4404).

Hexahydro-1*H*-imidazo[4,5-*g*]quinoline (**145**) was reacted with EMME in boiling DMF to give (imidazo[4,5-*g*]quinolin-5-yl)methylenemalonate (**146**) in 54% yield [79JAP(K)154797].



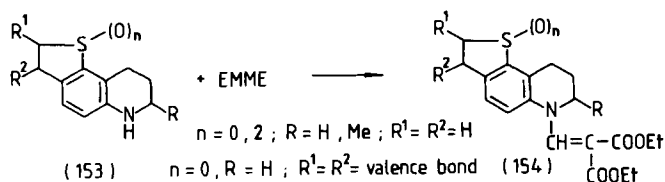
Benzo(*f*)quinoline (**147**) was reacted with EMME at 170°C for 3 hr to yield (benzo(*f*)quinolin-1-yl)methylenemalonate (**148**) (84USP4456606).

Tricyclic furo[3,2-*f*]- and thieno[3,2-*f*]quinolines (**149**, X = O, S) were treated with EMME at 120–150°C to give malonate derivatives (**150**, X = O, S) in good yields [79JAP(K)163598].

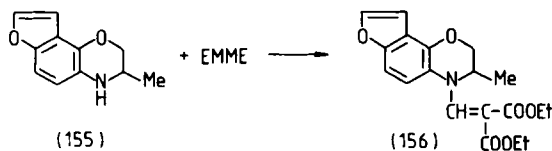


Furo[3,2-*f*]quinolines (**151**) were reacted with EMME at 120–130°C for 1.5–2.5 hr to give furoquinolinylmethylenemalonates (**152**) (84CPB4923).

Thieno[2,3-*f*]quinolines (**153**) were reacted with EMME at 130–140°C to afford 6-thienoquinolinylmethylenemalonates (**154**) in 66–89% yields (88AP241).



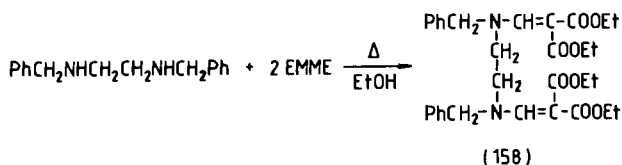
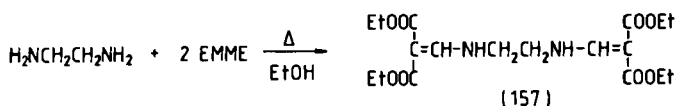
Furo[2,3-*h*]-1,4-benzoxazine (**155**) was reacted with EMME at 120–130°C for 40 min to yield furobenzoxazinylmethylenemalonate (**156**) (84CPB4923).



c. From Polyamines

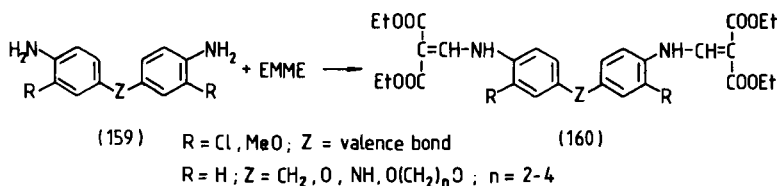
Depending on the reaction conditions and molar ratio, mono- and bis(aminomethylenemalonates) can be obtained in the reactions of dialkyl alkoxymethylenemalonates and bisamines.

The reaction of 1,2-diaminoethane and EMME was carried out in boiling ethanol or in a mixture of diethyl ether and ethanol at -5°C to give bis(aminomethylenemalonate) (**157**) in 72% and 64% yields (64JMC68; 67MI1).



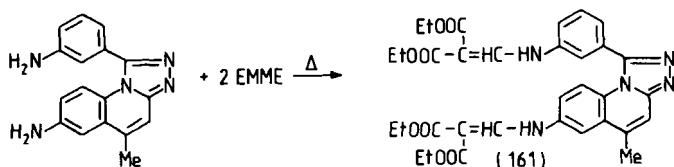
1,2-Bis(benzylamino)ethylene was reacted with 2 mol. equiv. of EMME in boiling ethanol to give bis(aminomethylenemalonate) (**158**) in 43% yield (64JMC68).

Bis(phenylamines) (**159**) were reacted with EMME to give bis(aminomethylenemalonates) (**160**) (64JMC68; 84MI1, 84MI5; 86MI12).

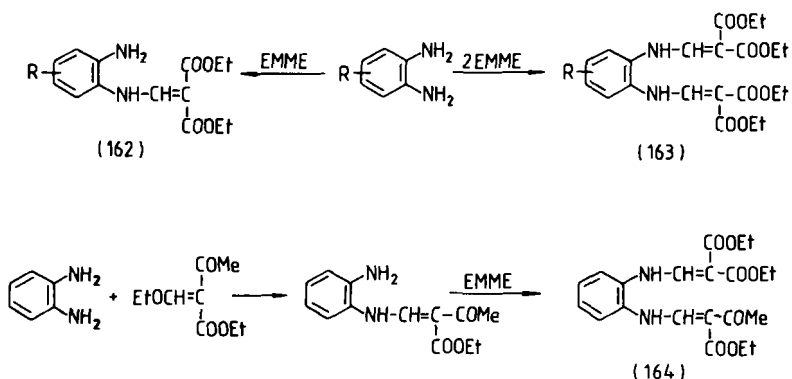


7-Amino-1-(3-aminophenyl)-5-methyl[1,2,4]triazolo[4,3-*a*]quinoline was reacted with EMME by heating on a steam-bath for 3 hr to give the corresponding bis(aminomethylenemalonate) (**161**) (86EUP174833).

The reaction of *o*-phenylenediamine (R = H) and 1 mol. equiv. of EMME at 100°C for 2 hr afforded diethyl *N*-(2-aminophenyl)aminomethylenemalonate (**162**, R = H) in 94% yield (57MI2; 59MI1). When 2 mol. equiv. of



EMME was applied and the reaction mixture was heated on a steam-bath for 4 hr, 1,2-bis(aminomethylenemalonate) (**163**, R = H) was obtained in 79% yield (46JA1320).

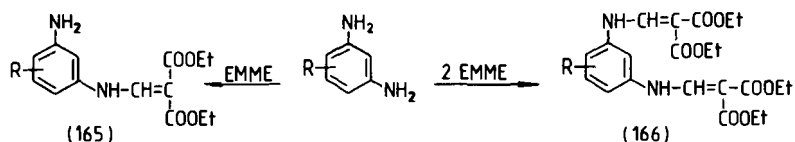


Diethyl *N*-(2-aminophenyl)aminomethylenemalonates (**162**, R = H, NO₂) were also prepared in boiling ethanol for 0.5 hr in 78–90% yields (67M11; 68AF1214). *o*-Phenylenediamines were reacted with 2 mol. equiv. of EMME at 140°C for 3.5 hr (78USP4123536) or at 100°C for 6 hr (67M11) to give 1,2-bis(aminomethylenemalonates) (**163**).

Further dialkyl 1,2-bis(aminomethylenemalonates) were prepared in a similar way (72GEP2220294; 81ZC286; 83JHC681).

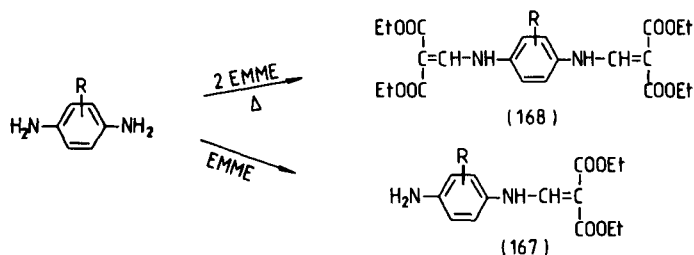
o-Phenylenediamine was first reacted with ethyl ethoxymethyleneacetate in ethanol, and the product was then reacted with EMME at room temperature to afford the aminomethylenemalonate derivative (**164**) in 75% yield (85ZC28).

(3-Aminophenyl)aminomethylenemalonates (**165**) and 1,3-bis(aminomethylenemalonates) (**166**) were prepared when *m*-phenylenediamines

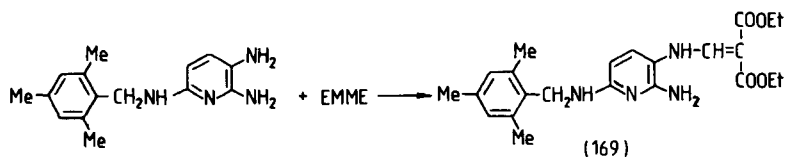


were reacted with 1 mol. equiv. (80MI2; 85EUP134165, 85FRP2548664; 86FRP2574404) and 2 mol. equiv. of EMME (54JA1109; 64JMC68; 72GEP2220294; 83JHC681; 86EUP174832), respectively.

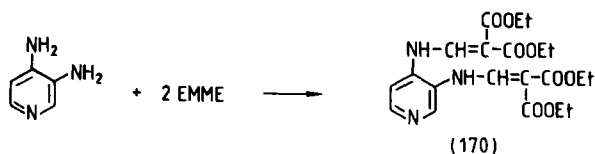
Depending on the molar ratio, the reactions of *p*-phenylenediamines and EMME gave *N*-(4-aminophenyl)aminomethylenemalonates (**167**) (86-EUP174832) or 1,4-bis(aminomethylenemalonates) (**168**) (49JCS1017; 86-EUP174832).



2,3-Diamino-6-[(2,4,6-trimethylphenyl)methylamino]pyridine was reacted with EMME in boiling dioxane for 30 min to give 3-pyridylamino-methylenemalonate (**169**) in 73% yield (79CZ387).

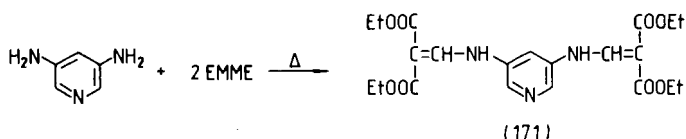


3,4-Diaminopyridine was reacted with 2 mol. equiv. of EMME at 100°C for 5 hr to give 3,4-bis(aminomethylenemalonate) (**170**) in 30% yield (59JA6297).

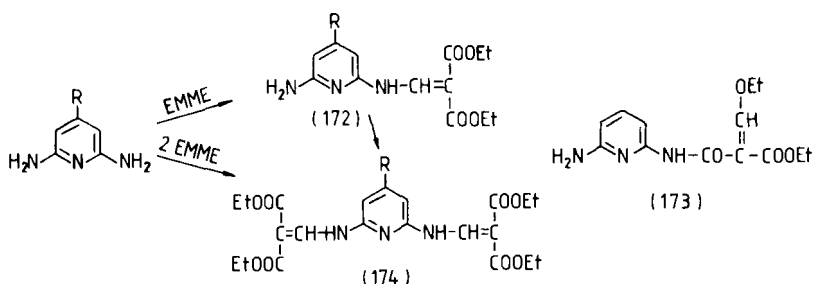


The reaction of 3,5-diaminopyridine and 2 mol. equiv. of EMME in the presence of a catalytic amount of concentrated hydrochloric acid at reflux

temperature for 45 min gave 3,5-bis(aminomethylenemalonate) (**171**) in 71% yield (78BAP509).



The reaction of a roughly 1 : 1 molar ratio of 2,6-diaminopyridine and EMME at 2°C for 3 hr gave *N*-(6-amino-2-pyridyl)aminomethylenemalonate (**172**, R = H) in 37% yield (65G1492), while when the reaction mixture was stirred in ethanol at 45–55°C for 25 min and then boiled for 10 min, the yield was 54% (62BEP612258). Originally, the structure of the product (**172**, R = H) was described incorrectly as **173** (65G1492; 71G129).

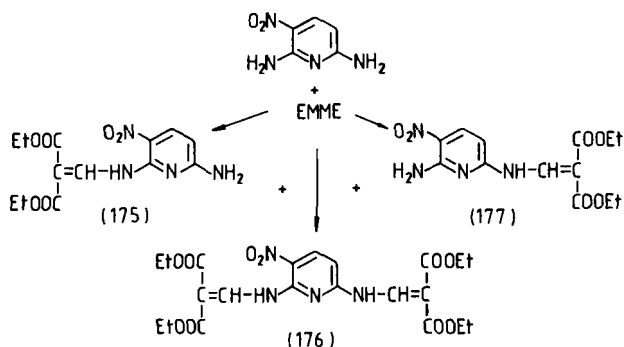


When 2,6-diaminopyridines (R = H, OEt) were reacted with 2 mol. equiv. of EMME by heating at 110°C for 30 min or at 250°C for 15–120 min, 2,6-bis(2,2-diethoxycarbonylvinylamino)pyridines (**174**) were obtained in 60–83% yields [65G1492; 70JHC875; 71JCS(C)2985; 86EUP174832]. Bis(aminomethylenemalonate) (**174**, R = H) was also prepared in 87% yield in the reaction of *N*-(6-amino-2-pyridyl)aminomethylenemalonate (**172**, R = H) and EMME at 3–5°C for 50 hr (65G1492).

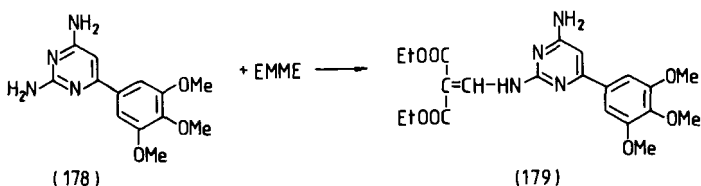
At times, the condensation products (**172** and **174**) were cyclized, without isolation, by further heating of the reaction mixture [46JA1317; 71JCS(C)2991].

After treatment of the reaction mixture of 2,6-diamino-3-nitropyridine and an excess of EMME at 120°C for 100 hr, 18% of bis(aminomethylenemalonate) (**176**) and 58% and 8% of aminomethylenemalonates (**175** and

177), respectively, were isolated (72G253). When the reaction was carried out at 140–150°C for 90 hr, 67% of bis(aminomethylenemalonate) (**176**) and 8% of aminomethylenemalonate (**177**) were obtained. Aminomethylenemalonates (**175** and **177**) could be converted to bis(aminomethylenemalonate) (**176**) by further treatment with EMME at 140°C.



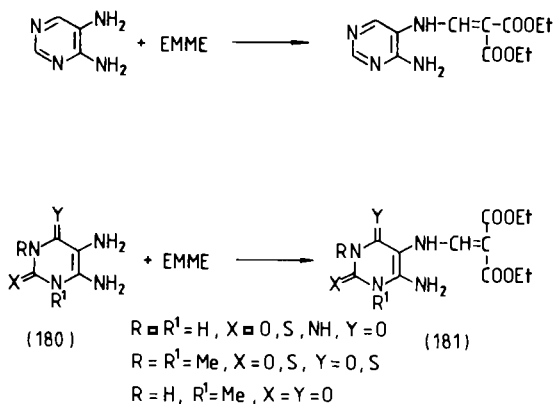
When trimethoprim (**178**) was reacted with EMME at 100°C for 1 hr, *N*-(4-amino-2-pyrimidinyl)aminomethylenemalonate (**179**) was obtained in 11% yield (79GEP2758115).



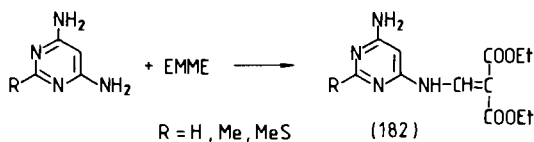
The reaction of 4,5-diaminopyrimidine and EMME in boiling ethanol for 30 min gave *N*-(4-amino-5-pyrimidinyl)aminomethylenemalonate in 79% yield (68AF1214).

4,5-Diaminopyrimidine derivatives (**180**) were reacted with EMME in boiling ethanol for 30 min, or by heating in DMF for 15–20 min, to give *N*-(4-amino-5-pyrimidinyl)aminomethylenemalonates (**181**) in 44–49% yields (68AF1214).

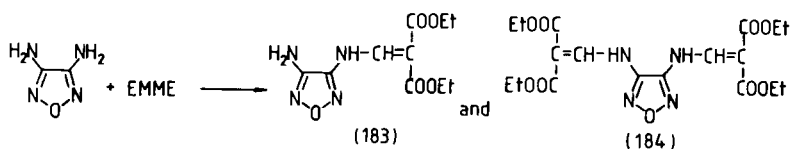
4,6-Diaminopyrimidines were reacted with EMME in boiling ethanol for 30 min (68AF1214) or for 180 min (70CPB1385), or at 135–165°C for 20–60 min (72JOC3980), to afford *N*-(6-amino-4-pyrimidinyl)aminomethylenemalonates (**182**) in 20–79% yields. Diethyl *N*-(4,6-diamino-5-



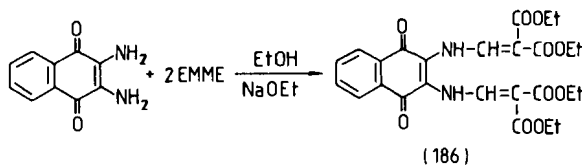
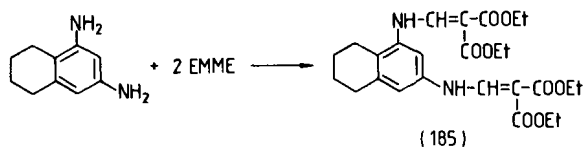
pyrimidinyl)aminomethylenemalonate was prepared in 86% yield in the reaction of 4,5,6-triaminopyrimidine and EMME in boiling ethanol for 30 min (68AF1214).



Depending on the molar ratio, mono- and biscondensation products (183 and 184) were obtained in 68% and 61% yields, respectively, in the reaction of 3,4-diamino-1,2,5-oxadiazole and EMME at 110–120°C for 5–10 min (79KGS319).

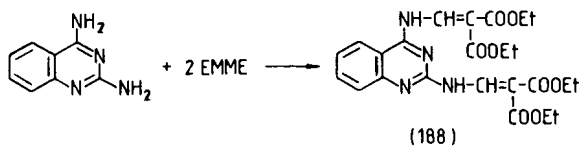
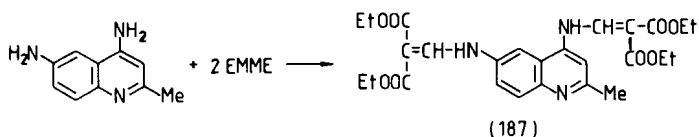


The reaction of 5,7-diamino-1,2,3,4-tetrahydronaphthalene and EMME at 100°C for 1 hr gave bis(aminomethylenemalonate) (**185**) (72GEP222-0294).



2,3-Diaminonaphthoquinone was reacted with 2 mol equiv. of EMME in ethanol in the presence of sodium ethylate at ambient temperature for 1 hr to give bis(aminomethylenemalonate) (**186**) in 28% yield (88LA799).

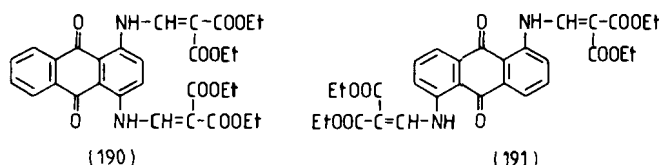
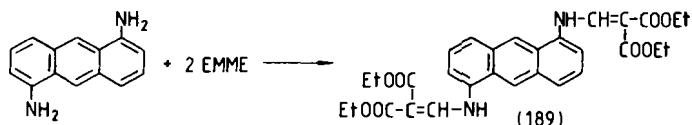
4,6-Bis(aminomethylenemalonate) (**187**) was prepared in the reaction of 4,6-diamino-2-methylquinoline and EMME (86EUP174832).



The reaction of 2,4-diaminoquinazoline and EMME was carried out in DMF at ambient temperature for 2 hr, and the reaction mixture was then

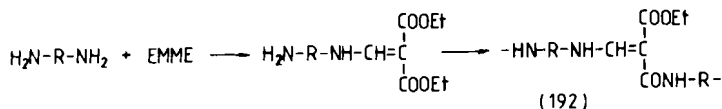
heated at 150°C for 45 min to give bis(aminomethylenemalonate) (**188**) in 19% yield (81EUP30156).

1,5-Diaminoanthracene was reacted with EMME in boiling xylene for 4 hr to afford bis(aminomethylenemalonate) (**189**) in 80% yield (62MI2).



Under similar conditions, 1,4-diamino- and 1,5-diaminoanthraquinones reacted with EMME to give bis(aminomethylenemalonates) (**190** and **191**) in 60% and 77% yields, respectively (59MI2).

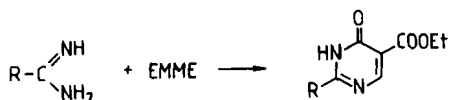
Poly(enaminoamide)-type polymers (**192**) were obtained in 89–97% yields when 1 : 1 mixtures of diamine (4,4'-methylenediphenyldiamine, *p*-phenylenediamine, or *o*-phenylenediamine) and EMME were heated in the presence of a solvent (*N*-methylpyrrolidone, trifluoroacetic acid, or *m*-cresol) or in the melt at 155–195°C under nitrogen for 2–12 hr (78MI2).



The reaction of 1,2,3,4,7,8,9,10-octahydro-1,7-phenanthridine and EMME at 140–150°C for 1.5 hr gave diethyl (1,2,3,4,7,8,9,10-octahydro-1,7-phenanthridin-1-yl)malonate in 87% yield (89MI2).

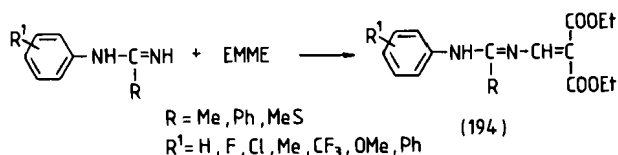
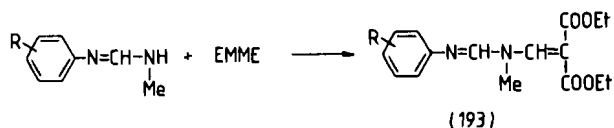
d. *From Amidines, Hydrazines, Amidrazones, (Thio)semicarbazides, Isothiosemicarbazones, Carboxamides, Carbohydrazides, (Thio)ureas, and Sulfamides.*

During the reactions of amidines and EMME, cyclocondensation usually occurs to give 4-(3*H*)-oxypyrimidine-5-carboxylates (e.g., 77MI5). Relevant literature is not treated in this review; it can be found in more specialized books (62MI1; 85MI1) (Scheme 23).



SCHEME 23

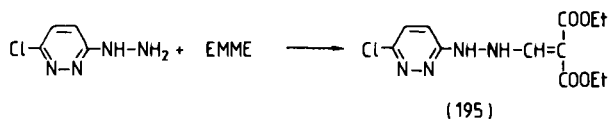
N-Methyl-*N'*-(substituted phenyl)formamidine was reacted with EMME in boiling toluene for 3 hr to give amidine derivatives (**193**) in poor yields (80EUP15440).



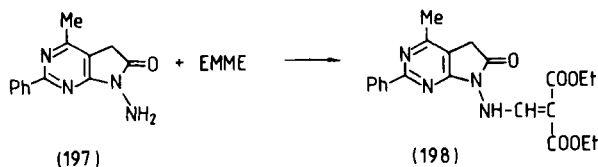
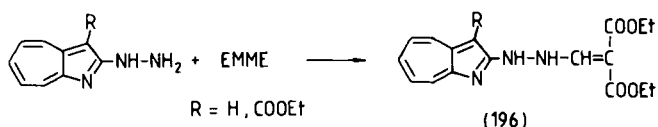
N-Arylamidines were condensed with EMME in boiling ethanol for 1.25–144 hr to afford condensation products (**194**) in 53–82% yields [82IJC(B)228].

3-Chloro-6-hydrazinopyridazine was reacted with EMME in DMF at 75–80°C for 20 min. After dilution of the reaction mixture with water, hydrazinomethylenemalonate (**195**) was obtained in 74% yield (80JHC-1527).

Arylhydrazines were reacted with EMME at ambient temperature for 24 hr to give hydrazinomethylenemalonates (87GEP33617554).

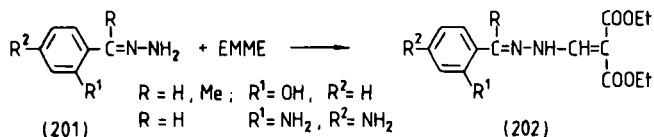
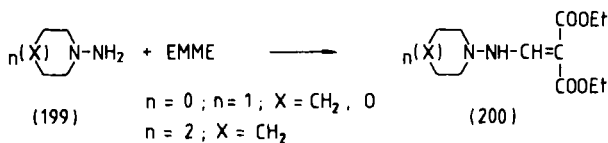


The reactions of 2-hydrazino-1-azaazulenes and EMME in boiling ethanol for 0.5–1.0 hr gave 2-(1-azaazulen-2-yl)hydrazinomethylenemalonates (**196**) in 92–96% yields (88BCJ1440).



Diethyl [2-(2,6-dichloro-4-trifluoromethylphenyl)hydrazino]methylenemalonate was prepared in 97% yield in the reaction of 2,6-dichloro-4-trifluoromethylphenylhydrazine and EMME in ethanol at 70–75°C for 5 hr (88GEP3728278).

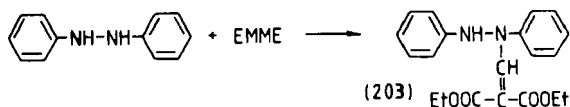
(Pyrrolopyrimidin-7-ylamino)methylenemalonate (**198**) was prepared in 29% yield in the reaction of the 7-amino derivative (**197**) and EMME in a



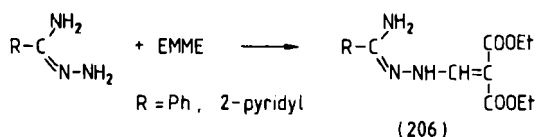
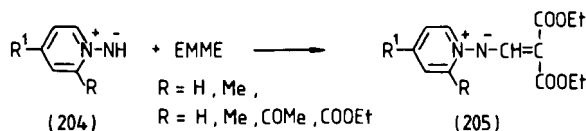
mixture of ethanol and *N,N*-dimethylacetamide at reflux temperature for 20 hr (75JHC1291).

The reactions of monocyclic *N*-aminoheterocycles (**199**) and EMME in methanol at room temperature for 1 hr gave the corresponding *N*-aminomethylenemalonates (**200**) in 95–98% yields (85JOC909; 87BSF365).

Hydrazone (**201**) were reacted with EMME in boiling ethanol for 1 hr to give condensation products (**202**) in 87–98% yields (64JMC68).



The reaction of *N,N'*-diphenylhydrazine and EMME in boiling ethanol for 1 hr afforded (*N,N'*-diphenylhydrazino)methylenemalonate (**203**) in 61% yield (64JMC68).

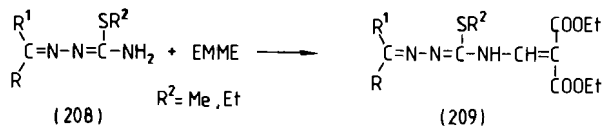
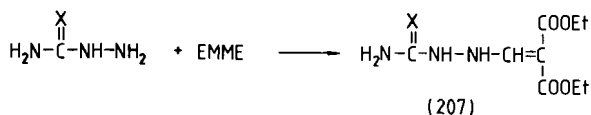


In the reaction of pyridine-*N*-imides (**204**) and EMME in ethanol at ambient temperature for 20–25 hr, ylides **205** were prepared in 56–78% yields [73JCS(P1)2580].

The reactions of amidrazones and EMME in ethanol at 0°C gave aminomethylenemalonates (**206**) in 71–78% yields (77BCJ957).

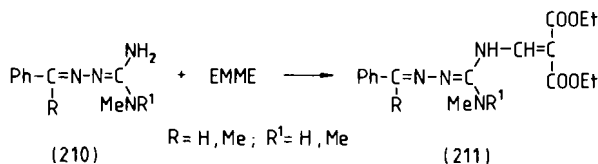
Semicarbazide and thiosemicarbazide were reacted with EMME in boiling ethanol for 1 hr to give aminomethylenemalonates (**207**, X = O, S) in 92 and 98% yields, respectively (64JMC68).

Isothiosemicarbazone derivatives (**208**) were reacted with EMME in boiling benzene for 4 hr to afford aminomethylenemalonates (**209**) in 43–96% yields [81BCJ1767, 81JOC3956; 85JOC5513; 88JCS(P1)1897]. For



the acetaldehyde derivative (**208**, R = H, R¹ = Me), a 95% yield was achieved when the reaction was carried out in boiling benzene in the presence of triethylamine for 6 hr (85JOC5513).

Diaminomethylenehydrazones (**210**) were reacted with EMME in benzene at room temperature for 1 day (when R¹ = H) or at reflux temperature for 3 hr (when R¹ = Me) to give aminomethylenemalonate derivatives (**211**) in 60–89% yields (88CPB1963).

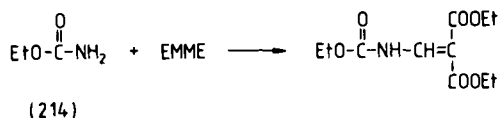
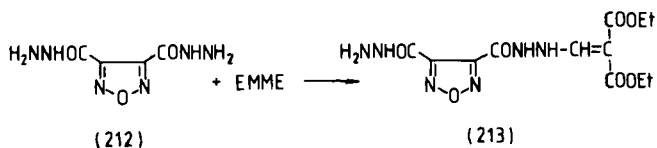


A 1 : 1 mixture of acetamide and EMME was heated during 3 hr. The temperature of the reaction mixture was gradually raised from 120°C to 180°C, while the ethanol formed was distilled off to give acetamidomethylenemalonate in 75% yield (76RC661) (Scheme 24). When this mixture was heated at 180°C for 2.5 hr, diethyl acetamidomethylenemalonate was obtained in 10% yield (64JMC68).

Condensation product (**213**) was prepared in 59% yield in the reaction of dihydrazide (**212**) and EMME in boiling ethanol for 15 min (79KGS319).



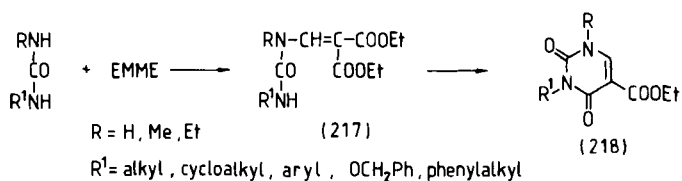
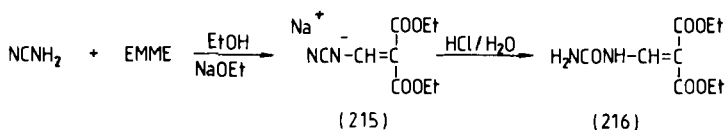
SCHEME 24

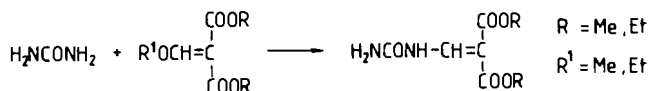


3-Oxomorpholine was reacted with EMME in boiling ethanol for 1 hr to afford (3-oxomorpholin-4-yl)methylenemalonate in 16% yield (64JMC68).

The reaction of a 1 : 1 mixture of urethane (214) and EMME, on heating at 180°C for 2.5 hr, gave ethoxycarbonylaminomethylenemalonate in 20% yield (64JMC68).

The reaction of cyanamide and EMME in ethanol in the presence of sodium ethoxide at ambient temperature for 24 hr gave the sodium salt of cyanaminomethylenemalonate (215) in 65% yield (76PHA536). The treatment of cyanaminomethylenemalonate with aqueous hydrochloric acid afforded (aminocarbonylamino)methylenemalonate (216) in 83% yield.





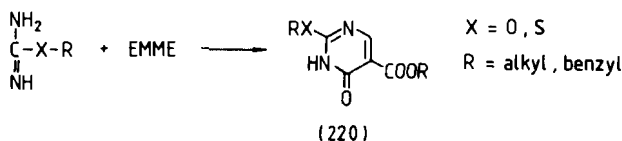
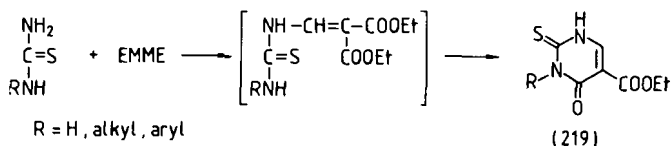
SCHEME 25

Earlier, urea was reacted with EMME in the presence of sodium ethylate in ethanol at ambient temperature for 7 days to give (aminocarbonylamino)methylenemalonate (**216**) in 22% yield (52JA4267). (Aminocarbonylamino)methylenemalonate (**216**) was not obtained when urea and EMME were heated at 140°C (07MI1).

The reactions of *N*-substituted and *N,N'*-disubstituted ureas and EMME were carried out at 120°C for 12 hr, to give the corresponding (aminocarbonylamino)methylenemalonates (**217**), which were then used in the following cyclization step without purification (52JA4267). Alternatively, the reactions were carried out in the presence of ethanolic sodium ethoxide to give the corresponding pyrimidine-5-carboxylates (**218**) (64M265; 80H769; 81CPB3181).

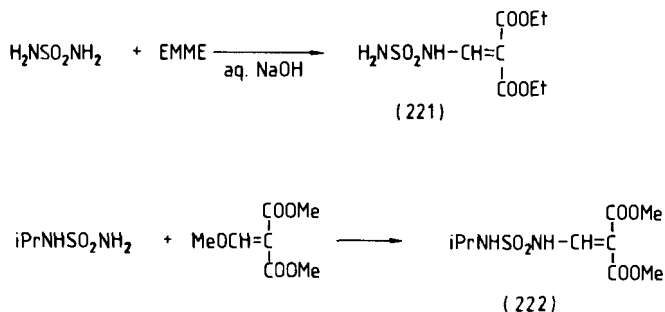
Urea was reacted with dialkyl alkoxymethylenemalonates in ethanol in the presence of 35% hydrochloric acid at room temperature for 3–4 days to afford dialkyl (aminocarbonylamino)methylenemalonates in 85–87% yields [79JAP(K)144320; 80JAP(K)104271] (Scheme 25).

Thiourea and its *N*-substituted derivatives readily reacted with EMME in hot ethanolic sodium ethoxide to yield 2-thiopyrimidine-5-carboxylates (**219**) (42JA794; 56JA5294). With *N*-substituted thiourea, as in the case of *N*-substituted urea, the primary amino group was first involved in the reaction.



O-Methylisouronium sulfate and *S*-alkylisothioureas were reacted with EMME in methanolic sodium methoxide or aqueous ethanol, respectively, to yield 2-methoxy- and 2-alkylthiopyrimidine-5-carboxylates (**220**) (07M12; 42JA794; 59M14; 62JOC3614; 87M19).

The treatment of a suspension of sulfamide and EMME with aqueous sodium hydroxide at room temperature for 12 hr gave sulfamidomethylenemalonate (**221**) in 41% yield (78JHC253).



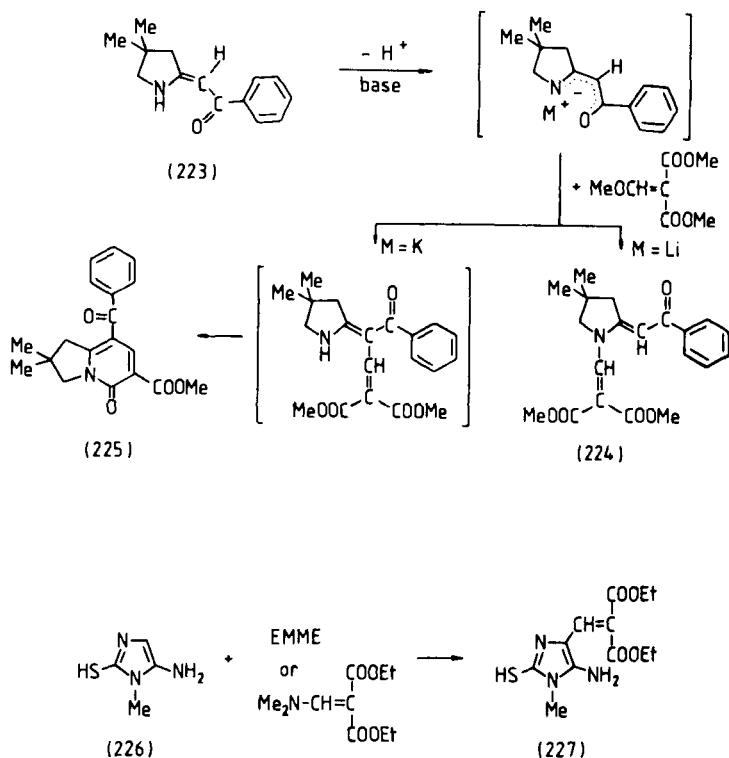
The reaction of isopropylsulfamide and dimethyl methoxymethylenemalonate in methanol in the presence of sodium methoxide for 3 days at ambient temperature afforded sulfamidomethylenemalonate (**222**) in 84% yield (79LA950).

Reactions between guanidines and EMME are discussed in Chapter 5, Section D.

e. Anomalous Reactions

When the reaction of enaminone (**223**) and dimethyl methoxymethylenemalonate was carried out in THF in the presence of butyllithium, pyrrolidinomethylenemalonate (**224**) was obtained in 4% yield. When this reaction conducted in DMF in the presence of potassium *tert*-butylate, pyrrolidinomethylenemalonate (**224**) and 2,3-dihydro-1*H*-indolizin-5-one (**225**) were prepared in 21 and 46% yields, respectively (88AP345).

Instead of the amino group, position 4 of the imidazole ring was involved in the reaction of 5-amino-2-mercapto-1-methylimidazole (**226**) and EMME when they were heated under nitrogen, giving 4-imidazolylmethylenemalonate (**227**) (78H241). The same product was obtained when the hydrochloride of imidazole (**226**) was reacted with *N,N*-dimethylaminomethylenemalonate in DMF or acetic acid.

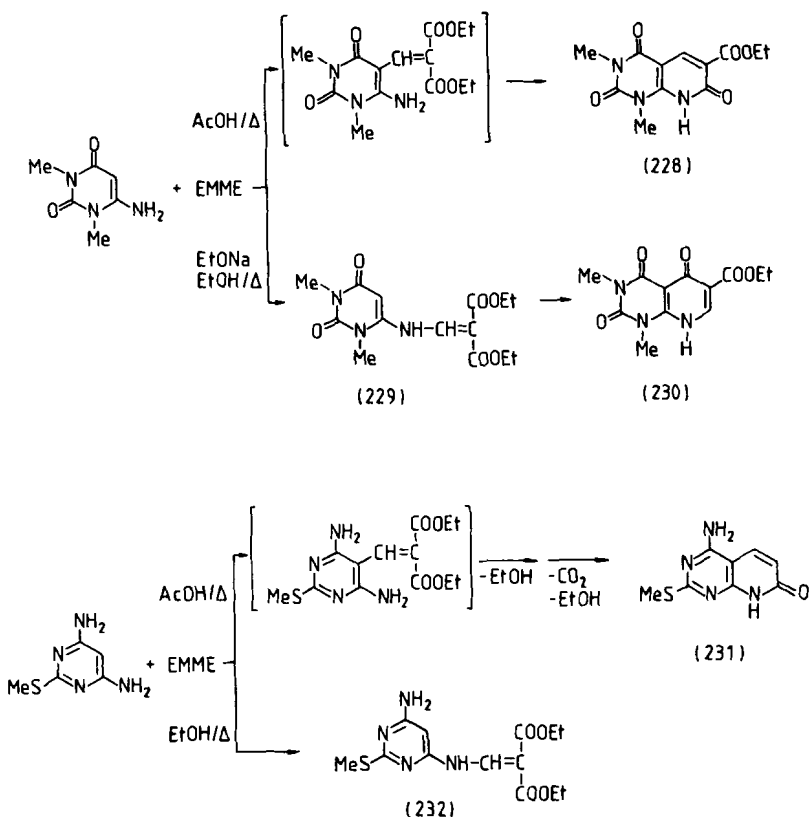


Regioselective reactions took place between 4-aminopyrimidines and EMME (70CPB1385; 72JOC3980; 76JOC1095; 85JHC1469, 85JHC1735; 87JHC1453; 89JHC1089).

The reaction of 6-amino-1,3-dimethylpyrimidine-2,4-dione and EMME in the melt at $210^\circ C$ gave 7-oxopyrido[2,3-*d*]pyrimidine (**228**) in 29% yield (76JOC1095), whereas in boiling acetic acid overnight, the yield was 85% (85JHC1469).

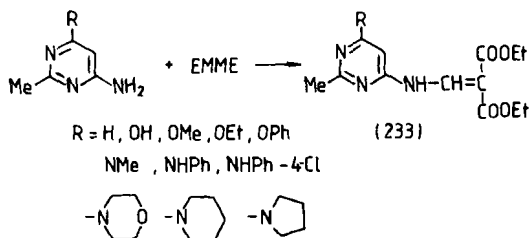
When the reaction was conducted under basic conditions, in boiling ethanol overnight in the presence of sodium ethoxide, diethyl 4-pyrimidinylaminomethylenemalonate (**229**) was obtained in 99% yield. Compound **229** could be cyclized to the isomeric 5-oxopyrido[2,3-*d*]pyrimidine (**230**) in 89% yield on boiling in diphenyl ether for 1 hr (85JHC1469).

The reaction of 4,6-diamino-2-methylthiopyrimidine and EMME in boiling acetic acid overnight gave 7-oxopyrido[2,3-*d*]pyrimidine (**231**) in 36% yield (85JHC1735), whereas in boiling ethanol overnight, this reaction afforded *N*-(6-aminopyrimidin-4-yl)aminomethylenemalonate (**232**) in 85%

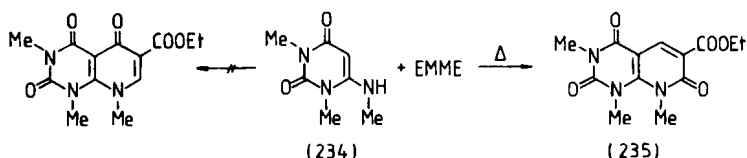


yield (85JHC1735). In the melt at 165°C for 40 min, the yield was 70% (72JOC3980).

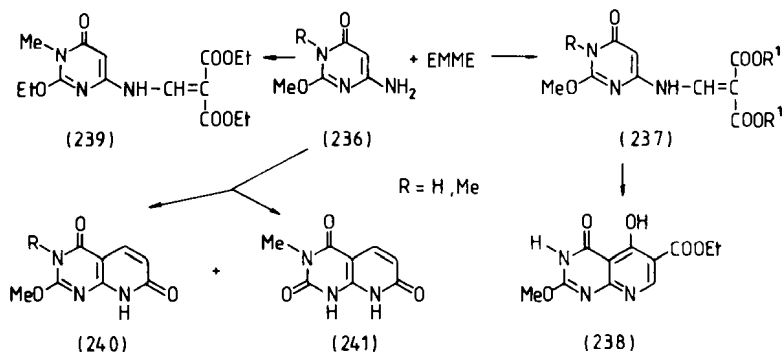
The reactions of 4-amino-2-methylpyrimidines and EMME at 110–180°C for 0.5–2.0 hr gave *N*-(2-methylpyrimidin-4-yl)aminomethylenemalonates (233) in 35–85% yields (70CPB1385).



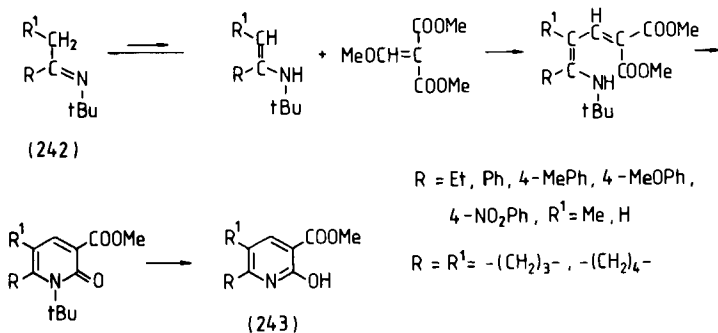
The cyclocondensation of 1,3-dimethyl-6-methylaminopyrimidine-2,4-dione (**234**) and EMME at 200–230°C for 8 hr gave 1,3,8-trimethyl-2,4,8-trioxypyrido[2,3-*d*]pyrimidin-6-carboxylate (**235**) in 39% yield (87JHC1453).



Reaction of 2-methoxy-6-aminopyridin-4-ones (**236**) and EMME gave, in 22–38% yields, 4-pyrimidinylaminomethylenemalonates (**237**, $R^1 = \text{Et}$) in the melt at 165–170°C for 2–3 hr or in boiling ethanol for 1–4 days (89JHC1089). When the condensations were carried out in boiling methanol in the presence of sodium methylate for 1 day, reesterification also occurred to give dimethyl esters of 4-pyrimidinylaminomethylenemalonates (**237**, $R^1 = \text{Me}$). Reactions in boiling ethanol in the presence of sodium ethylate afforded a mixture of 4-pyrimidinylaminomethylenemalonate (**237**, $R = \text{H}$, $R^1 = \text{Et}$) and pyrido[2,3-*d*]pyrimidinecarboxylate (**238**), starting from **236** ($R = \text{H}$). Under similar reaction conditions, a 2-ethoxy derivative of 4-pyrimidinylaminomethylenemalonate (**239**) could be obtained starting from compound **236** ($R = \text{Me}$). When reactions were carried out in boiling acetic acid, 68% of 4,7-dioxypyrido[2,3-*d*]pyrimidine (**240**, $R = \text{H}$) and 7% of **237** ($R = \text{H}$, $R^1 = \text{Et}$) were obtained from **236** ($R = \text{H}$). Thirteen percent of 2,4,7-trioxypyrido[2,3-*d*]pyrimidine (**241**), 5% of 4,7-dioxypyrido[2,3-*d*]pyrimidine (**240**, $R = \text{Me}$), and 29% of **237** ($R = \text{Me}$, $R^1 = \text{Et}$) were also isolated from the reaction mixture of **236** ($R = \text{Me}$).



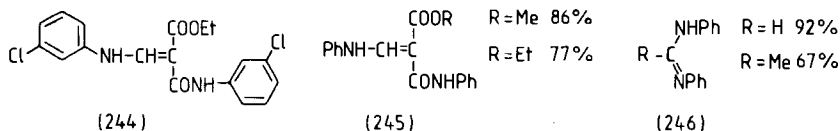
When Schiff's bases (**242**), derived from ketones and *tert*-butylamine, were reacted with dimethyl methoxymethylenemalonate in diphenyl ether at 80–130°C for 1–15 hr, then at 190–250°C for 1–3 hr, 2-hydroxy-3-pyridinecarboxylates (**243**) were obtained by a one-pot procedure. In the first step of the reaction, the beta-carbon of the enamine moiety was involved instead of the amino group (89JHC773).



2. ONE-POT SYNTHESSES

In the previous section, aminomethylenemalonates were obtained in the reactions of amines and alkoxymethylenemalonates. The latter were prepared in a separate step from dialkyl malonates and alkyl orthoformate. Aminomethylenemalonates can also be synthesized in a "one-pot" procedure, starting directly from the amine, dialkyl malonate, and alkyl orthoformate or its equivalent.

Snyder and Jones obtained ethyl *N*-(3-chlorophenyl)aminomethylenemalonate (**244**) in 77% yield when 2 mol of 3-chloroaniline was reacted with 1 mol of diethyl malonate and 1 mol of ethyl orthoformate at 160–165°C. The ethanol formed during the reaction was distilled off (46JA1253).

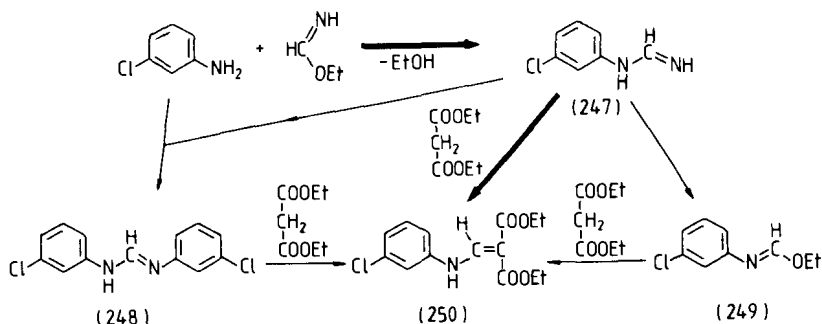


Wolfbeis investigated the reactions of amines and orthoesters with different CH-acid molecules (81CB3471). When the reactions of aniline, ethyl orthoformate, and dialkyl malonates (2 mol) were carried out at 130–140°C for 4 hr, phenylaminomethylenemalonates (**245**) were obtained (81CB3471). Similar reactions with aliphatic amines were unsuccessful. Phenylaminomethylenemalononic acid could not be prepared in the reactions of aniline, methyl orthoformate or orthoacetate, and malonic acid. When these reactions were carried out in 2-propanol, only amidines (**246**) were obtained.

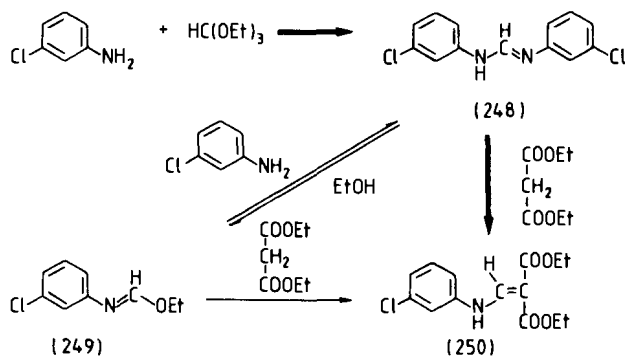
Egri *et al.* investigated the "one-pot" synthesis of *N*-(3-chlorophenyl)-aminomethylenemalonate (**250**), starting from equimolar amounts of 3-chloroaniline, diethyl malonate, and ethyl formimidate hydrochloride or ethyl orthoformate (73ACH217). The reaction involving ethyl formimidate hydrochloride was conducted in the presence of triethylamine at 120–130°C for 2 hr and then at 140°C for 80 hr. The ethanol formed in the reaction was continuously distilled off. *N*-(3-Chlorophenyl)aminomethylenemalonate (**250**) was obtained in 98–99% yields.

When these reactions were monitored by means of thin-layer chromatography, the initial formation of an amidine (see Schemes 26 and 27, **247** or **248**) could be detected. The amidine then either reacted directly with diethyl malonate or was converted into another reactive intermediate, *N*-arylformimidate (**249**), which next reacted with diethyl malonate to give *N*-(3-chlorophenyl)aminomethylenemalonate (**250**).

In the case of ethyl formimidate hydrochloride, only a small amount of symmetrically substituted *N,N'*-diarylformamidine (**248**) could be detected. Because of the higher reactivity of the unsymmetrically substituted compound (**247**), a shorter reaction period could be applied.



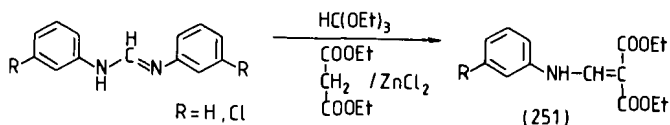
SCHEME 26



SCHEME 27

N-(3-Chlorophenyl)aminomethylenemalonate (250) was also prepared in 95% yield when a mixture of *N,N'*-bis(3-chlorophenyl)formimidate (0.5 mol) (248), diethyl malonate (1.8 mol), and ethyl orthoformate (0.55 mol) was heated at 130°C for 10 hr in the presence of a catalytic amount of ZnCl_2 or MgCl_2 . The ethanol formed in the reaction was distilled off (73MIP1).

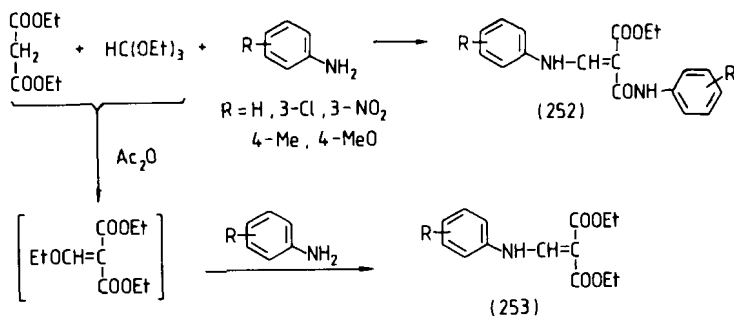
Anilines were first reacted with ethyl orthoformate to give *N,N'*-diarylformamidines, which were then treated with a second batch of ethyl orthoformate and diethyl malonate in the presence of ZnCl_2 to afford arylaminomethylenemalonates (251) (86MIP1).



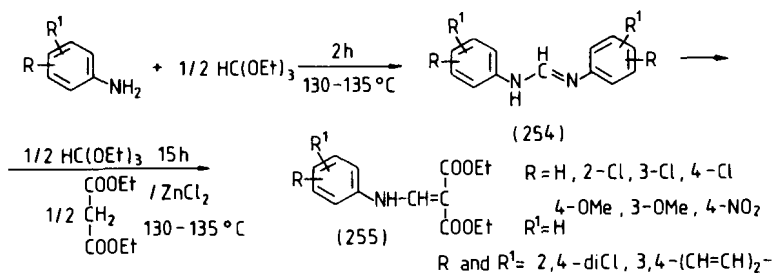
The uncatalyzed reactions between anilines, ethyl orthoformate, and diethyl malonate afforded ethyl arylaminomethylenemalonates (252) in 67–85% yields (87SC549). However, if the malonate was first reacted with ethyl orthoformate and acetic anhydride in the presence of a catalytic amount of ZnCl_2 at boiling temperature for 5 hr and aniline was then added to the reaction mixture, reflux being maintained for 0.5 hr, arylaminomethylenemalonates (253) were obtained in 52–85% yields.

It was claimed that arylaminomethylenemalonates were obtained in the reactions of anilines, malonate, and ethyl orthoformate (76USP3981717).

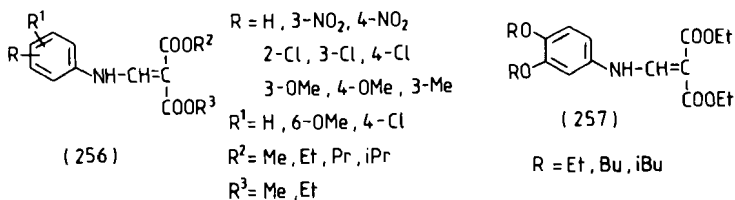
Ayyangar *et al.* prepared a number of arylaminomethylenemalonates (255) in 86–96% yields by starting from arylamines, ethyl orthoformate,



and diethyl malonate (820PP327). They reacted the arylamine with half of the stoichiometric quantity of ethyl orthoformate at 130–135°C for 2 hr, and the intermediate bis(aryl)formamidine that formed (254) (without isolation) was treated with the second half of the ethyl orthoformate and half of the stoichiometric quantity of diethyl malonate in the presence of a catalytic amount of anhydrous ZnCl_2 for 5 hr at 130–135°C. Finally, the remaining diethyl malonate was added, and the reaction mixture was stirred for 15 hr under identical conditions to give arylaminomethylenemalonate (255).



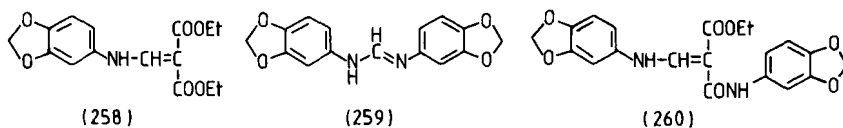
The reactions of anilines, alkyl orthoformate, and dialkyl malonates in the presence of FeCl_3 catalysts at 100–140°C for 6 hr gave dialkyl arylaminomethylenemalonates (256) in very good yields (87MIP3; 88OPP93).



Guo *et al.* prepared *N*-(3-chloro-4-fluorophenyl)aminomethylenemalonate (**256**, $R = 3\text{-Cl}$, $R^1 = 4\text{-F}$, $R^2 = R^3 = \text{Et}$) in 60–70% yields when 3-chloro-4-fluoroaniline was reacted with triethyl orthoformate and diethyl malonate in the presence of a Lewis acid. From the reaction mixture, ethyl *N*-(3-chloro-4-fluorophenyl)-2-[(3-chloro-4-fluorophenyl)-aminomethylene]malonamate and *N*-(3-chloro-4-fluorophenyl)formanilide were also isolated as byproducts (88M13).

Egri *et al.* prepared *N*-(3,4-dialkoxyphenyl)aminomethylenemalonates (**257**) in over 90% yields in the reactions of 3,4-dialkoxyanilines, ethyl formimidate hydrochloride and diethyl malonate in the presence of triethylamine (70MIP3). The reaction mixtures were gradually heated to 120°C for 2 hr and were then reacted at 140°C for 10 hr, while the ethanol formed was continuously distilled off. These phenylaminomethylenemalonates (**257**) were also prepared in over 93% yields in the reactions of 3,4-dialkoxyanilines, ethyl orthoformate, and diethyl malonate in the presence of catalytic amounts of water at 140°C for 60 hr.

N-(3,4-Methylenedioxyphenyl)aminomethylenemalonate (**258**) was prepared in 81% yield by heating a 1 : 1 : 1 mixture of 3,4-methylenedioxyaniline, ethyl orthoformate, and diethyl malonate in the presence of ZnCl_2 at 120–140°C for 4 hr [73JAP(K)15879].

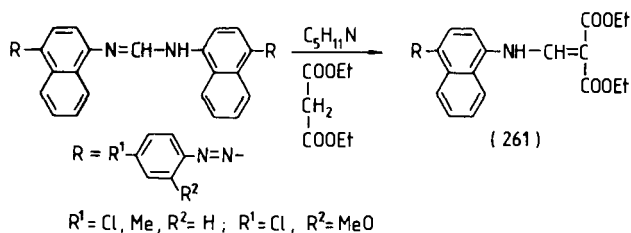


When a mixture of 3,4-methylenedioxyaniline, ethyl formimidate, and diethyl malonate was reacted at 110–120°C for 6 hr, 30% of diethyl malonate and 19% of 3,4-methylenedioxyaniline were recovered. In addition, 18% of *N*-(3,4-methylenedioxyphenyl)aminomethylenemalonate (**258**), 11% of formamidine (**259**), and 7% of *N*-(3,4-methylenedioxyphenyl)amino-methylenemalonamate (**260**) were isolated from the reaction mixture by means of column chromatography (74M12).

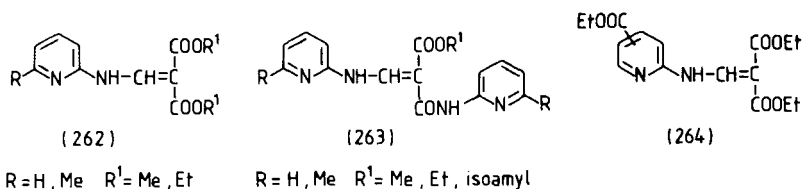
Labeled *N*-(3,4-methylenedioxyphenyl)aminomethylenemalonate (**258**) was obtained in 54% yield after column chromatography when a 1.2 : 1 : 1.2 mixture of 3,4-methylenedioxyaniline, diethyl ^{14}C -malonate, and ethyl orthoformate was reacted at 122–125°C for 7.5 hr in the presence of anhydrous ZnCl_2 (74M12).

4-Arylazo-1-naphthylamines were first reacted with ethyl orthoformate in boiling xylene for 2 hr; diethyl malonate and piperidine were then slowly added to the reaction mixture over a period of 15–20 min. The resulting

solutions were refluxed for 5 hr to give 1-naphthylaminomethylenemalonates (**261**) in 72–75% yields (80M11).



A mixture of 2-amino-6-methylpyridine, ethyl orthoformate, and diethyl malonate was heated at 150°C for 1 hr to give *N*-(6-methyl-2-pyridyl)-aminomethylenemalonate (**262**, R = 6-Me, R¹ = Et) in 77% yield [74JAP(K)88879].



2-Pyridylaminomethylenemalonates (**262**) were prepared in over 90% yields in the reactions of 2-aminopyridines, ethyl orthoformate, and dialkyl malonates at 130°C for 3–6 hr (73GEP2227651; 87SC549).

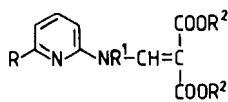
Under similar reaction conditions, radioactive *N*-(6-methyl-2-pyridyl)aminomethylenemalonate was prepared by starting from diethyl (¹⁴C-carboxyl)malonate (75M12).

In the uncatalyzed condensations of 2-aminopyridines, alkyl orthoformate, and dialkyl malonate at 110°C, 2-pyridylaminomethylenemalonates (**263**, R = H, Me; R¹ = Me, Et) were obtained in 20–25% yields. When isoamyl orthoformate was applied, a 5.2:4.8 mixture of ethyl and isoamyl *N*-(6-methyl-2-pyridyl)aminomethylenemalonates (**263**, R = Me, R¹ = Et and isoamyl) was isolated in 90% yield (87SC549).

The reactions of ethyl 2-aminopyridine-4- and -5-carboxylates, ethyl orthoformate, and diethyl malonate in the presence of ZnCl₂ at 100–120°C for 15 min afforded 2-pyridylaminomethylenemalonates (**264**) in 53–71% yields (78M15).

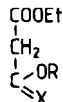
2-Pyridylaminomethylenemalonates (**265**) were prepared in 40–60% yields in the reactions of 2-aminopyridines (R¹ = H) and 2-(alkylamino)-

pyridines ($R^1 = \text{Et, Pr, decyl}$), ethyl orthoformate, and dialkyl malonates at 150–155°C for 5 hr and then at 160–170°C for 1 hr [74JAP(K)270].



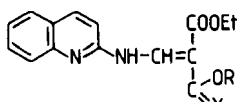
(265)

$R = \text{Me, Et, Pr, decyl}$
 $R^1 = \text{H, Et, Pr, decyl}$
 $R^2 = \text{Me, Et}$



(266)

$X = \text{O, R} = \text{H}$
 $X = \text{S, R} = \text{Et}$



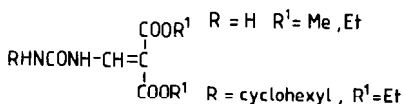
(267)

N-Ethyl-*N*-(6-methyl-2-pyridyl)aminomethylenemalonate (**265**, $R = \text{Me}$, $R^1 = R^2 = \text{Et}$) was prepared in 16–66% yields in the reaction of 2-(ethylamino)-6-methylpyridine, diethyl malonate, and ethyl orthoformate in the presence of acidic catalysts (AcOH, EtCOOH, Dianion WK-11) at 150–160°C for 2–3.5 hr [74JAP(K)109383].

The monoethyl *N*-(6-methyl-2-pyridyl)aminomethylenemalonate was prepared in 34% yield in the reaction of monoethyl malonate, ethyl orthoformate, and 2-amino-6-methylpyridine in the presence of catalytic amounts of AlCl_3 at 110–115°C for 45 min (72AF815).

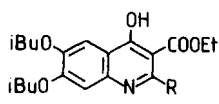
2-Quinolylaminomethylenemalonates (**267**) were prepared in the reactions of 2-aminoquinoline, ethyl orthoformate, and malonic acid derivatives (**266**) in the presence of AlCl_3 at 135–140°C for 30 min (74MIP1).

The reactions of urea, dialkyl malonates, and alkyl orthoformates at reflux temperature for 10 hr gave dialkyl ureidomethylenemalonates (**268**, $R = \text{H}$) in 40% yield (53JA671), while in the reaction at 130°C for 4 hr the yield was 66–69% [77JAP(K)131529; 81CPB3181].



(268)

$R = \text{H, R}^1 = \text{Me, Et}$
 $R = \text{cyclohexyl, R}^1 = \text{Et}$
 $R = \text{cyclohexyl, R}^1 = \text{H, Et}$



(269)

$R = \text{Me, Ph}$

The reaction of cyclohexylurea, ethyl orthoformate, and malonic acid overnight gave *N*-cyclohexylureidomethylenemalononic acid (**268**, $R = \text{cyclohexyl}$, $R^1 = \text{H}$) in 92% yield (53JA671).

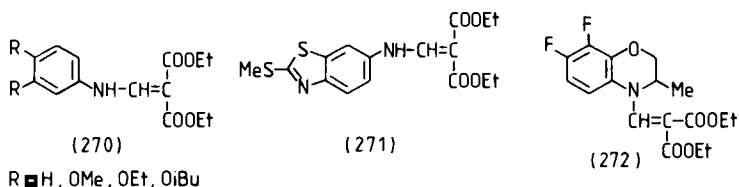
The reaction of *N*-tetrahydropyranylurea, ethyl orthoformate, and diethyl malonate or malonic acid at 85°C for 7 days afforded *N*-tetrahydropy-

ranylureidomethylenemalonic acid derivatives (**268**, R = tetrahydropyranyl, R¹ = H, Et) (80H769).

In the reactions of equimolar amounts of 3,4-diisobutoxyaniline, diethyl malonate, and ethyl imidate hydrochlorides in the presence of triethylamine at 120°C for 2 hr and then at 140°C for 15 hr, 2-substituted quinoline-3-carboxylates (**269**) were prepared (73ACH217).

3. FROM AMINOMETHYLENEMALONATES

The reactions of diethyl *N,N*-dimethylaminomethylenemalonate and anilines in acetic acid at ambient temperature for 8–10 hr gave arylaminomethylenemalonates (**270**) in 57–84% yields (70GEP1936758; 71S220).



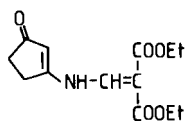
6-Benzothiazolylaminomethylenemalonate (**271**) was prepared in 77% yield in the reaction of 6-amino-2-methylthiobenzothiazole and diethyl *N,N*-dimethylaminomethylenemalonate in acetic acid at 70–80°C for 5 hr (76CPB130). The same product (**271**) was obtained in 85% yield in the reaction of 6-aminobenzothiazole and EMME in Dowtherm A at 110–130°C for 1 hr.

Diethyl *N*-hetarylaminomethylenemalonates were prepared in good yields in the reactions of diethyl *N,N*-dimethylaminomethylenemalonate and 5-aminoimidazole, 5-aminoisothiazole or 2-aminothiophene hydrochlorides in DMF or acetic acid at 20–80°C for 1–5 hr [77JAP(K)116460].

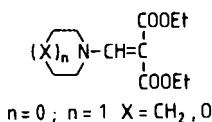
Diethyl *N,N*-dimethylaminomethylenemalonate was reacted with benzylamine in ethylene glycol to give diethyl *N*-benzylaminomethylenemalonate in 90% yield (81ZOR2421).

Diethyl *N,N*-dimethylaminomethylenemalonate was reacted with 7,8-difluoro-3-methyl-1,4-benzoxazine in acetic acid at 80–90°C for 5 hr to give (1,4-benzoxazin-4-yl)methylenemalonate (**272**) in 74.8% yield [86JAP(K)246172, 86JAP(K)246188].

1-Amino-1-cyclopenten-3-one was reacted with diethyl aminomethylenemalonate (**13**) in the presence of a catalytic amount of *p*-toluenesulfonic acid at 120–130°C for 39 hr to afford *N*-(3-oxocyclopenten-1-yl)aminomethylenemalonate (**273**) in 14% yield (75JHC1245).

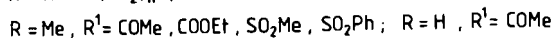
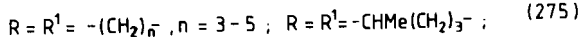
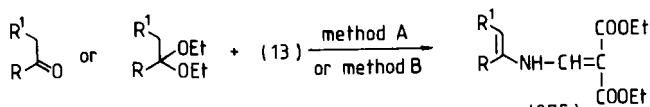


(273)

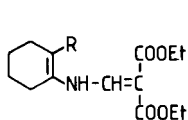


(274)

Diethyl aminomethylenemalonate (**13**), formed in the reaction of diethyl malonate and *s*-triazine in boiling ethanol, was reacted with piperidine, morpholine, or pyrrolidine in boiling ethanol for 1–3 hr to give *N*-(1-azacycloalk-1-yl)methylenemalonates (**274**) in 74–78% yields (76T2603; 77AP353).

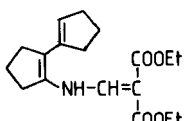


N-Substituted aminomethylenemalonates (**275**) were obtained in 5–56% yields in the reactions of diethyl aminomethylenemalonate (**13**) and ketones or ketals in the presence of phosphorus pentoxide in THF at room temperature for 1–5 days (method A) or by heating in the presence of a small amount of *p*-toluenesulfonic acid in *o*-xylene for 15–22 hr (method B) (75JHC1245). Methyl ethyl ketone and acetophenone did not react under these conditions. Under the conditions of method B, 2-methylcyclohexanone gave *N*-(2-methylcyclohexen-1-yl)aminomethylenemalonate (**276**, *R* = Me) in 36% yield. Cyclohexanone diethyl ketal and diethyl aminomethylenemalonate (**13**) were reacted at 140°C for 35 hr (method C) to give *N*-(cyclohexen-1-yl)-aminomethylenemalonate (**276**, *R* = H) in 35% yield (75JHC1245). When cyclopentanone was reacted with diethyl

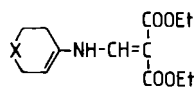


(276)

R = H, Me

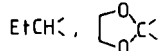


(277)



(278)

X = O, S, NCOOEt, MeCH<



aminomethylenemalonate (**13**) under the conditions of method A, only *N*-[2-(1-cyclopentenyl)cyclopenten-1-yl]aminomethylenemalonate (**277**) in 8% yield could be isolated from the reaction mixture.

Other variations of condensation agents (ethanolic hydrochloric acid, ZnCl_2 in THF, Triton B in dioxane, using AlCl_3 , TiCl_4 , or molecular sieves) to promote the reaction of cyclopentanone and diethyl aminomethylenemalonate (**13**) were unsuccessful (75JHC1245).

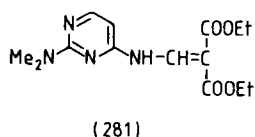
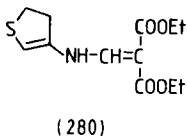
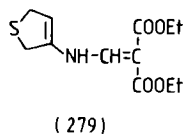
The reactions of diethyl aminomethylenemalonate (**13**) and phenyl ketones (R and $\text{R}^1 = \text{Me}$, Ph) on heating in xylene or decalin in the presence of a catalytic amount of *p*-toluenesulfonic acid at $175\text{--}185^\circ\text{C}$ for 24 hr gave *N*-substituted aminomethylenemalonates (**275**, $\text{R} = \text{Me}$, Ph and $\text{R}^1 = \text{Ph}$; $\text{R} = \text{Ph}$ and $\text{R}^1 = \text{Me}$) in 14–52% yields [77JHC477; 78JAP(K)63382].

Cycloalkanones were reacted with diethyl aminomethylenemalonate (**13**) in boiling toluene or xylene in the presence of dichloroacetic acid or *p*-toluenesulfonic acid monohydrate under nitrogen or argon for 2.5–7 days, and under a water separator, to give *N*-(1-cycloalkenyl)aminomethylenemalonates (**275**, $\text{R} = \text{R}^1 = -(\text{CH}_2)_n-$, $n = 6\text{--}10$) (88EUP270494).

Diethyl aminomethylenemalonate (**13**) was reacted with tetrahydrothiopyran-4-one in boiling toluene for 48 hr in the presence of *p*-toluenesulfonic acid to give *N*-(thiopyran-4-yl)aminomethylenemalonate (**278**, $\text{X} = \text{S}$) (86EUP168350; 87USP4647566).

Similar reactions were carried out with 4*H*-tetrahydropyran-4-one, 1-ethoxycarbonyl-4-piperidone, 4-alkylcyclohexanones, and 1,4-dioxaspiro[4.5]decan-8-one to give the corresponding aminomethylenemalonates (**278**, $\text{X} = \text{O}$, NCOOEt , MeCH , EtCH , $(\text{CH}_2\text{O})_2\text{C}$) (86EUP168350; 87USP4647566).

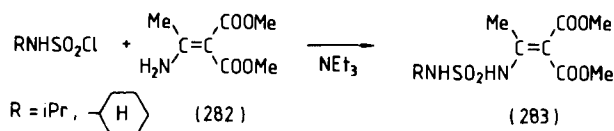
3-Oxotetrahydrothiophene was condensed with diethyl aminomethylenemalonate in boiling toluene for 60 hr in the presence of *p*-toluenesulfonic acid monohydrate under a Dean–Stark water collector to give a 1 : 1 mixture of *N*-(2,5- and 4,5-dihydro-3-thienyl)aminomethylenemalonates (**279** and **280**) (87USP4647566).



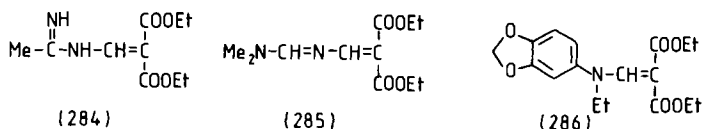
4-Chloro-2-(dimethylamino)pyrimidine was reacted with diethyl aminomethylenemalonate in ethanol in a sealed tube at 140°C for 6 hr to give 4-pyrimidinylaminomethylenemalonate (**281**) in 73% yield (72USP3673184).

Dimethyl 1-aminoethylidenemalonate (**282**) was reacted with sulfa-

moyl chlorides in toluene in the presence of triethylamine to afford *N*-substituted 1-aminoethylidenemalonates (**283**) in 60–62% yields (79LA950).



The reaction of diethyl aminomethylenemalonate (**13**) and methyl aceti-
midate in ethanol at room temperature for 24 hr gave an acetimidine
derivative (**284**) (59BCJ188).

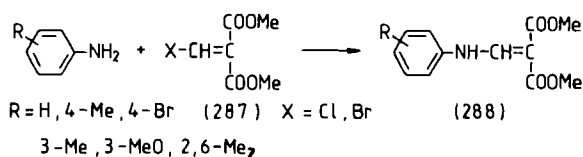


The reaction of diethyl aminomethylenemalonate (**13**) and *N,N*-
dimethylformamide diethyl acetal in boiling acetic acid gave diethyl *N*-
(dimethylaminomethylene)aminomethylenemalonate (**285**) in 64% yield
(87KFZ1249).

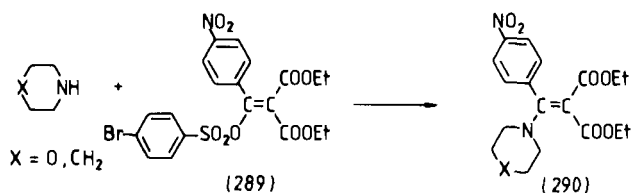
N-Ethyl-*N*-(3,4-methylenedioxy)aminomethylenemalonate (**286**) was
prepared in 64% yield via the reaction of *N*-(dimethylaminomethylene)ami-
nomethylenemalonate (**285**) and *N*-ethyl-3,4-methylenedioxyaniline in
boiling acetic acid for 5–10 min (87KFZ1249).

4. FROM DIALKYL HALOMETHYLENEMALONATES

The reaction of 1 mol of dimethyl chloromethylenemalonate (**287**,
X = Cl) and 2 mol of anilines in acetonitrile at ambient temperature for
1 hr gave arylaminomethylenemalonates (**288**) in 20–50% yields
[72JCS(P2)1823].

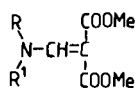


Diethyl amino(4-nitrophenyl)methylenemalonates (**290**) were prepared in 50–60% yields in similar reactions, starting from diethyl (4-nitrophenyl)(4-bromophenylsulfonyloxy)methylenemalonate (**289**) and morpholine or piperidine.

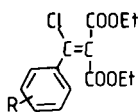


Rapport and Topol investigated the displacement of the halogen of bromo- and chloromethylenemalonates (**287**; X = Br, Cl) by several substituted anilines and that of the brosyloxy group of (4-nitrophenyl)(4-bromophenylsulfonyloxy)methylenemalonate (**289**) by morpholine and piperidine, in acetonitrile. A rate-determining nucleophilic addition of the amines was suggested as the mechanism for these reactions. Activation parameters (ΔH^\ddagger , ΔS^\ddagger) were determined [72JCS(P2)1823].

Dimethyl *N,N*-disubstituted aminomethylenemalonates (**291**) were prepared in 35–82% yields by the addition of dimethyl chloromethylenemalonate (**287**, X = Cl) in diethyl ether to an ethereal solution of secondary aliphatic or cyclic amines in the presence of triethylamine at 0–5°C, after which the reaction mixtures were stirred at ambient temperature (78T2315).

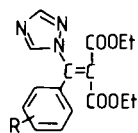


(291)

R = R¹ = Et, iPrR = R¹ = (CH₂)_n n = 2, 5

(292)

R = 4-Me, 2-Cl, 4-Cl, 2,6-diCl, etc



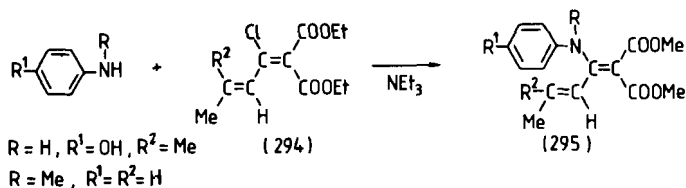
(293)

Dimethyl chloromethylenemalonate (**287**, R = Cl) was reacted with 2 mol of amines in acetonitrile at room temperature for 24 hr. The reaction mixtures were filtered and the filtrates were evaporated in vacuo to give aminomethylenemalonates [**291**, R = R¹ = (CH₂)_n, n = 4, 5; R = H, R¹ = *tert*-Bu, 4-ClPh, cyclohexyl] in 58–80% yields (79RRC1143).

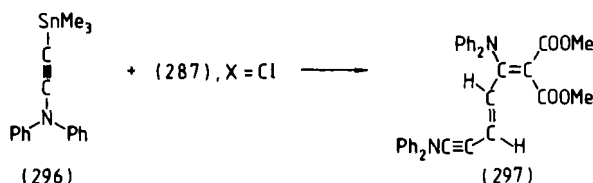
Diethyl chloro(substituted phenyl)methylenemalonates (**292**) were reacted with 1,2,4-triazole in boiling acetonitrile in the presence of potassium

carbonate to give (1,2,4-triazol-1-yl)(substituted phenyl)methylenemalonates (**293**) in good yields (80GEP2908377).

Diethyl chloro(1-propenyl)methylenemalonates (**294**) were reacted with anilines in the presence of triethylamine in toluene at 85°C for 12 hr, or in the absence of a solvent at 90°C for 12 hr, to give (substituted phenylamino)(1-propenyl)methylenemalonates (**295**) in moderate yields (88JOC880).

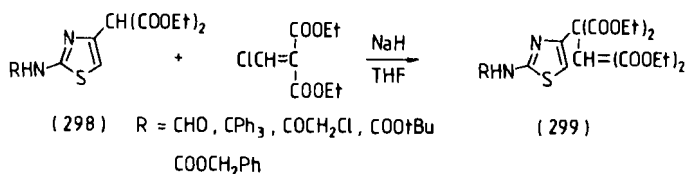


To a solution of dimethyl chloromethylenemalonate (1 mol) (**287**, $\text{X} = \text{Cl}$) in diethyl ether at -50°C , a solution of amine (2 mol) (**296**) was added dropwise, and the reaction mixture was then stirred at ambient temperature for 2 hr to give aminomethylenemalonate (**297**) in 8% yield (85LA2206).



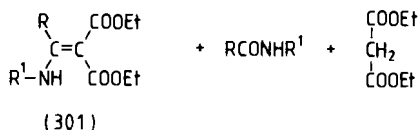
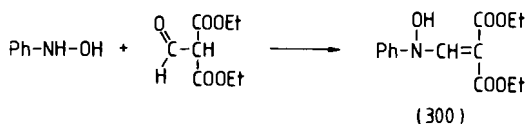
Dialkyl chloro(dialkylamino)methylenemalonates were reacted with diethyl phosphite to give dialkyl (dialkoxyphosphinyl)(dialkylamino)methylenemalonates (84MI3).

The reaction between the sodium salt of diethyl 2-[2-(*N*-substituted amino)-4-thiazolyl]malonate (**298**) and diethyl chloromethylenemalonate in THF at ambient temperature for 1–10 hr occurred on the central carbon atom of the malonate (**298**), not on the amino group, to give tetraesters (**299**) in 10–70% yields (86EUP168025).



5. FROM DIALKYL 2-ACYLMALONATES

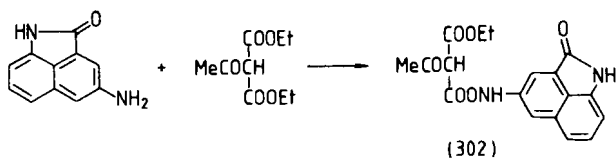
The reaction of *N*-phenylhydroxylamine and diethyl formylmalonate in 60% aqueous methanol at room temperature gave *N*-hydroxy-*N*-phenylaminomethylenemalonate (**300**) (25JCS1748).



Generally, the reactions of amines and 2-acylmalonates afforded not only the corresponding 1-(substituted amino)alkyldenemalonates (**301**), but also carboxamides and diethyl malonate (39JA2890; 54JIC711; 77GEP2705446).

If anilines were reacted with diethyl 2-acetylmalonate in nitrobenzene at 230–235°C for 1 hr, 3-acetyl-2,4-dihydroxyquinolines were obtained in 60–63% yields (46JA324).

Gould and Jacobs obtained a 70% yield of 1-(phenylamino)ethylidenemalonate (**301**, R = Me, R¹ = Ph) with 30% of acetanilide (R = Me, R¹ = Ph) in the reaction of diethyl 2-acetylmalonate (R = Me) and aniline at ambient temperature for 3 days (39JA2890). However, in the reaction of acetylmalonate and 3-aminonaphthostyryl at ambient temperature for several months, only 2-acetylmalonamate (**302**) was obtained (39JA2890).

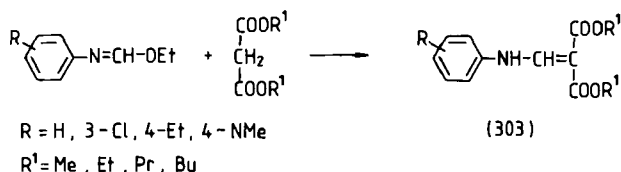


1-(2-Trifluoromethylphenylamino)ethylidenemalonate (**301**, R = Me, R¹ = 2-CF₃Ph) was prepared in 51% yield in the reaction of diethyl acetylmalonate and 2-trifluoromethylaniline at 100°C for 1 hr (77GEP2705446).

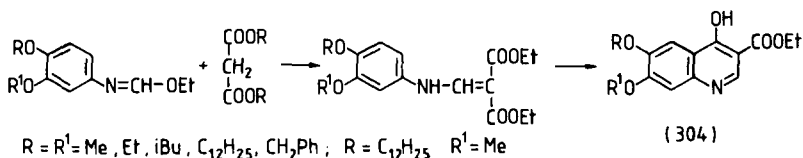
Diethyl 2-benzoylmalonate was reacted with anilines to give diethyl (arylamino)phenylmethylenemalonates (**6**, R = H, 2-Me, 4-Me, 4-Cl) in 28–38% yields (54JIC711).

6. FROM *N*-(HET)ARYLFORMIMIDATES

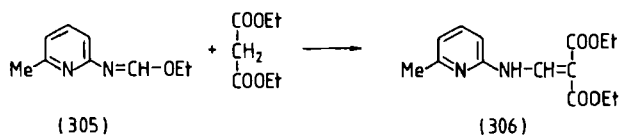
Arylaminomethylenemalonates (**303**) were obtained in 82–95% yields in the reactions of dialkyl malonates and *N*-arylformimidates in the presence of a catalytic amount of base (piperidine, sodium methylate, or potassium acetate) at 95–105°C for 24–30 hr (53USP2638480).



6,7-Dialkoxyquinoline-3-carboxylates (**304**) were prepared in 59–79% yields when diethyl malonate and *N*-arylformimidates were reacted in the presence of a catalytic amount of *N,N*-dimethylaniline at 120–150°C. The reaction mixtures were then diluted with paraffin oil preheated to 150°C and finally heated at 270°C for 15–30 min (72ACH351).



N-(6-Methyl-2-pyridyl)aminomethylenemalonate (**306**) was obtained in 86% yield in the reaction of a 1:1 mixture of *N*-(6-methyl-2-pyridyl)-formimide (**305**) and diethyl malonate at 150°C for 1 hr [74JAP(K)93370].

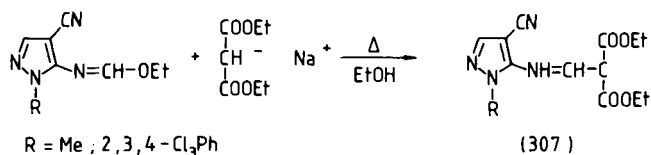


2-Amino-6-methylpyridine was reacted with ethyl orthoformate in the presence of acetic acid at 80–110°C for 1.5 hr to give formimide (**305**),

which was reacted with diethyl malonate in the presence of sodium acetate and acetic acid at 130°C. In this reaction, the ethanol formed was continuously distilled off to give *N*-(6-methyl-2-pyridyl)aminomethylenemalonate (**306**) in excellent yield (83MIP1).

A similar reaction was carried out starting from 3,4-methylenedioxyaniline to afford *N*-(3,4-methylenedioxyphenyl)aminomethylenemalonate (**258**) in 83% yield (83MIP2).

The sodium salt of diethyl malonate was reacted with 1-substituted 4-cyano-5-(ethoxymethyleneamino)pyrazoles in boiling ethanol for 1 hr to give *N*-(5-pyrazolyl)aminomethylenemalonates (**307**) in 30% and 60% yields (76CPB3120; 86EUP174832).



7. FROM AMIDINES

Dans obtained arylaminomethylenemalonamates (**252**) when *N,N'*-bisarylmidines were reacted with diethyl malonate at 150°C for 2–3 hr (02CB2496). Under these reaction conditions, the primarily formed arylaminomethylenemalonates (**253**) reacted further with anilines to give arylaminomethylenemalonamates (**252**). Later, more arylaminomethylenemalonamates (**252**) were similarly prepared (09JA1148; 13JA970; 46JA1251; 49BRP627297).

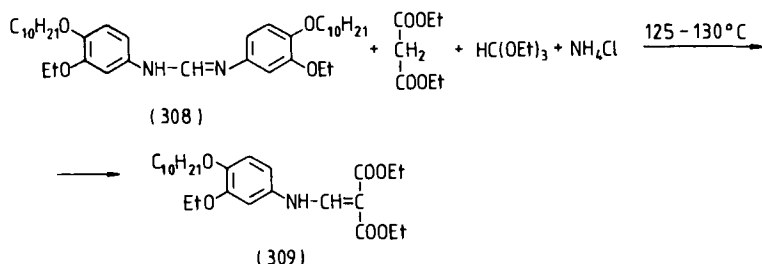
This route was not applicable for the preparation of 2- and 4-nitrophenyl derivatives of **252** (R = 2-NO₂, 4-NO₂), as the amidines obtained from 2- and 4-nitroanilines were not soluble in diethyl malonate (49JOC277).

Under carefully controlled reaction conditions, arylaminomethylenemalonates (**253**) could also be prepared (46JA1255; 49JOC277; 50USP2494801; 52USP2614121; 53USP2638480; 65EGP39681, 65MIP1; 66JOC4003; 73MIP1). When the reaction was carried out at lower temperature (103–118°C) for 3–13 hr, arylaminomethylenemalonates (**253**) could be isolated, but they also contained small quantities of arylaminomethylenemalonamates (**252**) (46JA1255; 49JOC277; 50USP2494801; 52USP2614121). Fischer reacted *N,N'*-bis(3-chlorophenyl)formamidine (**248**) and diethyl malonate in boiling benzene for 16 hr (50USP2494801). Ammonium nitrate was applied as an effective promoter in the latter reaction (63MII).

Sodium methylate, potassium acetate, and piperidine were also applied as catalysts in the reactions of amidines and dialkyl malonates (53USP2638480).

N-(3-Chlorophenyl)aminomethylenemalonate (**250**) was obtained in pure form in 94% yield when *N,N'*-bis(3-chlorophenyl)formamidine (**248**) (1 mol), diethyl malonate (1 mol), and ethyl orthoformate (1.2 mol) were reacted for 20 hr at 126°C, the ethanol evolved being continuously distilled off. More diethyl malonate (1 mol) was then added to the half-converted reaction mixture, and the reaction mixture was stirred at 126°C for 48 hr (65MIP1; 66JOC4003). Under these conditions, the formation of *N*-(3-chlorophenyl)aminomethylenemalonate (**252**, R = 3-Cl) could be excluded because the 3-chloroaniline formed in the reaction of amidine and malonate was simultaneously converted to amidine by ethyl orthoformate.

N-(3-Ethoxy-4-decyloxyphenyl)aminomethylenemalonate (**309**) was prepared in the reaction of the amidine (**308**), diethyl malonate, and ethyl orthoformate in the presence of ammonium chloride at 125–130°C for 1 hr (68FRP1531495). The crude ester (**309**) was applied without purification in the cyclization step.

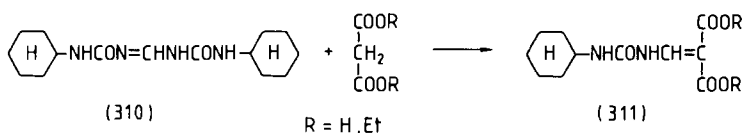


Starting from the appropriate amidines (**254**, R = 3-Cl, R¹ = H, and R = R¹ = 3,4-diisobutyl), diethyl malonate and ethyl orthoformate, *N*-(3-chlorophenyl)- and *N*-(3,4-diisobutylphenyl)aminomethylenemalonates (**250** and **257**, R = diisobutyl) were prepared in 92% yields, respectively (69MIP1).

N-(6-Methyl-2-pyridyl)aminomethylenemalonate (**306**) was prepared in 94% yield in the reaction of *N,N'*-bis(6-methyl-2-pyridyl)formamidine and diethyl malonate in the presence of ethyl orthoformate at 150°C for 1 hr, the ethanol formed being removed [74JAP(K)101380].

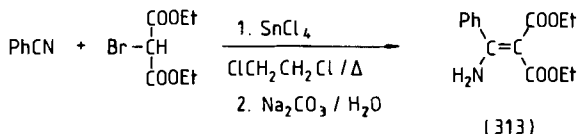
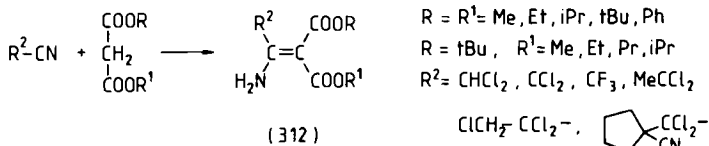
N-(6-Methyl-2-pyridyl)aminomethylenemalonate (**306**) was also obtained in 95% yield in the reaction of *N,N*-dimethyl-*N'*-(6-methyl-2-pyridyl)formamidine and diethyl malonate at 100–130°C for 12–50 hr (76MIP2) or in 47–53% yields in acetic acid at 130–150°C for 45–60 min (84URP1097620).

N,N'-Bis(cyclohexylaminocarbonyl)formamidine (**310**) was reacted with diethyl malonate in ethanol at 70°C for 60 hr to give *N*-(cyclohexylaminocarbonyl)aminomethylenemalonate (**311**, R = Et) in 24% yield (53-JA671). The similar reaction of malonic acid at room temperature for 3–4 min afforded (cyclohexylaminocarbonyl)aminomethylenemalonic acid (**311**, R = H) in 65% yield. When bis(cyclohexylaminocarbonyl)formamidine (**310**) was reacted with 1 : 1 molar mixture of diethyl malonate and malonic acid in ethanol at 70°C for 5 min, only malonic acid (**311**, R = H) was obtained, in 76% yield.



8. FROM NITRILES AND DIALKYL MALONATES

The reactions of dialkyl malonates and halogenated acetonitrile or propionitrile in the presence of sodium or sodium hydride for 2–3 hr gave the corresponding (halogenated 1-aminoalkylidene)malonates (**312**) in 38–96% yields (58CB1049; 64JOC707; 64USP3121108; 65JPR239; 68ZOR1710; 72MI2; 75ZOB873).



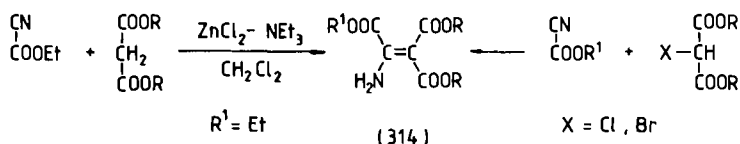
Dimethyl malonate was reacted with nitriles in boiling 1,2-dichloroethane in the presence of SnCl₄ for 26–50 min to give white crystalline products, which were treated with aqueous sodium carbonate to afford dimethyl aminomethylenemalonates (**312**, R = R¹ = Me, R² = Me, Et, Ph, CH=CHPh, CH=CHMe) in 17–57% yields (85TL2603). Earlier di-

ethyl malonates, nitriles, and SnCl_4 were reacted at 110–120°C for 5 min to give the corresponding diethyl 1-aminoalkylidenemalonates (67JAP7894; 68JAP17168).

Under the previous conditions, diethyl (amino)phenylmethylenemalonate (**313**) was also obtained in 35% yield in the reaction of diethyl bromomalonate and benzonitrile (85TL2603).

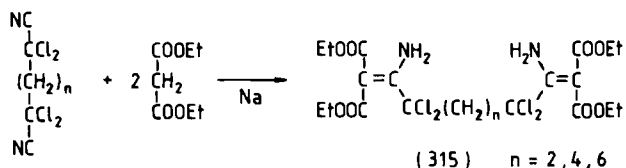
The reaction of 3-nitrobenzonitrile ($\text{R}^2 = 3\text{-NO}_2\text{Ph}$) and dimethyl malonate in the presence of SnCl_4 in boiling 1,2-dichloroethane for 1 hr gave dimethyl amino(3-nitrophenyl)methylenemalonate (**312**, $\text{R} = \text{R}^1 = \text{Me}$; $\text{R}^2 = 3\text{-NO}_2\text{Ph}$, $\text{R}^1 = 3\text{-NO}_2\text{C}_6\text{H}_4$) in 66% yield (87EUP228845).

The reactions of ethyl cyanoformate and dialkyl malonates in the presence of zinc chloride and triethylamine, or in the presence of TiCl_4 or SnCl_4 in methylene chloride at reflux temperature for 3 hr, or at room temperature overnight, gave amino(alkoxycarbonyl)methylenemalonates (**314**, $\text{R}^1 = \text{Et}$) in good yields [79TL2525; 81JAP(K)71050].



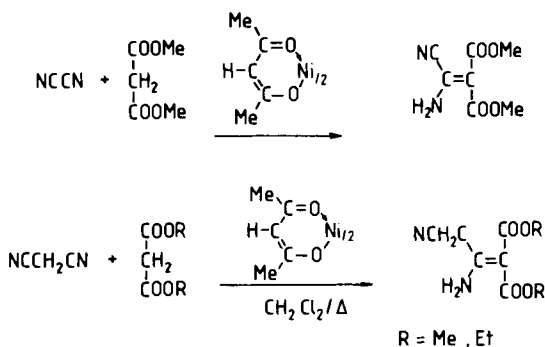
Amino(alkoxycarbonyl)methylenemalonates (**314**) were also prepared in good yields in the reactions of dialkyl cyanoformate and bromo- or chloromalonates in the presence of SnCl_2 or TiCl_3 in benzene, or in the presence of zinc activated by copper in THF, [81JAP(K)71049, 81JAP(K)87542].

Tetraesters (**315**) were prepared in 75–82% yields in the reactions of dinitriles and diethyl sodiomalonate at 70°C (68ZOR1710).



Dimethyl amino(cyano)methylenemalonate was prepared in the reaction of cyanogen and dimethyl malonate in the presence of $\text{Zn}(\text{acac})_2$ catalyst (82MI3).

The reaction of cyanogen and dimethyl malonate was also carried out in methylene chloride at ambient temperature for 300 hr in the presence



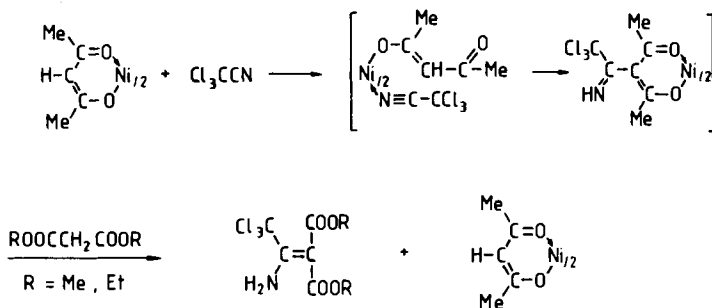
SCHEME 28

of $\text{Ni}(\text{acac})_2$ catalyst [84JCS(P2)965], or in toluene at room temperature for 150 hr in the presence of $\text{Zn}(\text{acac})_2$ catalyst (84JOC4696), to give dimethyl amino(cyano)methylenemalonate in 15–20% and 29% yields, respectively.

The reactions of malononitrile and dialkyl malonates in the presence of $\text{Ni}(\text{acac})_2$ as catalyst in boiling chloroform under nitrogen afforded (2-cyano-1-aminoethylidene)malonates in about 22% yields (86MI11) (Scheme 28).

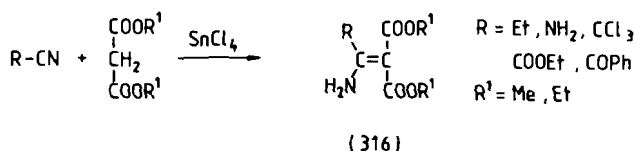
Dialkyl malonates were reacted with trichloroacetonitrile in methylene chloride in the presence of $\text{Ni}(\text{acac})_2$ catalyst under nitrogen at room temperature for 3 hr to give dialkyl (2,2,2-trichloro-1-aminoethylidene) malonates in 65% and 80% yields (86MI5) (Scheme 29).

The SnCl_4 -promoted reactions of dialkyl malonates with nitriles in boiling benzene or toluene for 2–4 hr, or at ambient temperature for



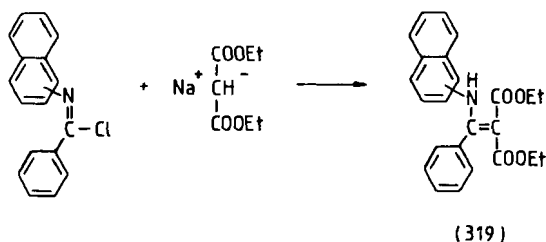
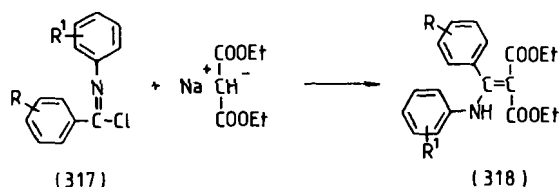
SCHEME 29

24–48 hr, under nitrogen gave aminomethylenemalonates (**316**), usually in high yields [88JCR(S)246].



9. FROM IMIDOYL CHLORIDES AND IN VILSMEIER-HAACK AND SIMILAR REACTIONS

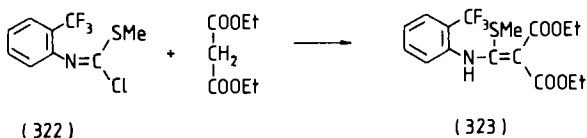
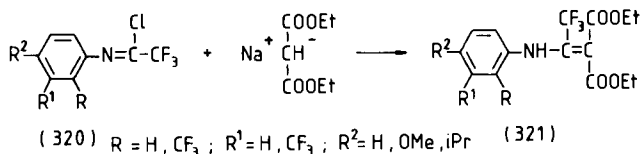
This type of reaction was first applied by Just in 1885, but the yields of aminomethylenemalonates (**318**) were poor, and the reactions were accompanied by the formation of a byproduct (see Chapter II).



Shah and Heeramanek improved the yields (30–45%) of **318** when mixtures of imidoyl chlorides (**317**), diethyl malonate, and diethyl sodiomalonate in 1 : 1 : 1 molar ratio were reacted in toluene at reflux temperature for 2 hr (36JCS428). This modification was later applied by others too (46JA1272; 49JIC171). Diethyl (naphthylamino)phenylmethylenemalonates (**319**) were also prepared in 18% and 30% yields by starting from *N*-(1- and 2-naphthyl)imidoyl chlorides (37JCS867).

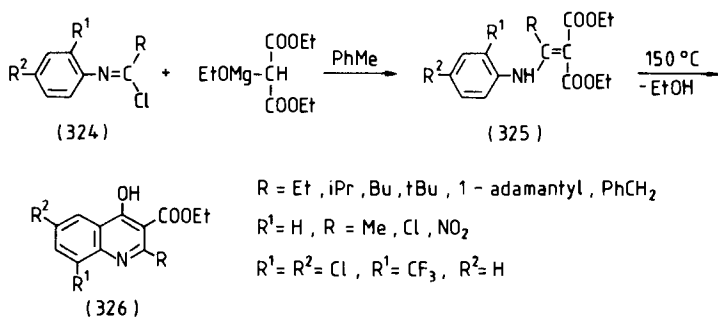
The aminomethylenemalonates (**318** and **319**) were usually cyclized without purification.

The sodium salt of diethyl malonate was reacted with imidoyl chlorides (**320**) in boiling toluene for 4 hr, or in DMF at ambient temperature for 1–3.5 hr, to give 1-(arylamino)-2,2,2-trifluoroethylidenemalonates (**321**) in 51–99% yields (80EUP12639).

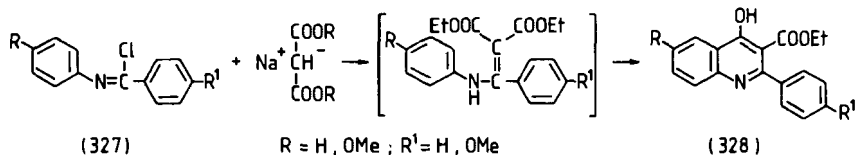


Diethyl malonate was reacted with imidoyl chloride (**322**) in DMF in the presence of sodium hydride at 95–100°C for 30 min to give methylthio(2-trifluoromethylphenylamino)methylenemalonate (**323**) in 40% yield (84FRP2532939).

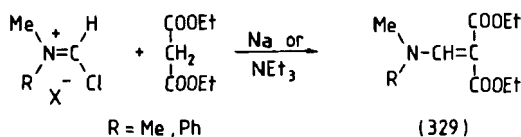
1-(Arylamino)alkylidenemalonates (**325**) were prepared in higher yields when imidoyl chlorides (**324**), prepared from the appropriate amide and phosphoryl chloride, were reacted with diethyl ethoxymagnesiummalonate in toluene at room temperature or at the boiling point for 0.5–8 hr (73JMC875; 77GEP2705446; 78FRP2377400). After removal of the toluene, the crude aminoalkylidenemalonates (**325**) were cyclized by heating to 2-substituted quinoline-3-carboxylates (**326**) in 68–83% yields.



Seka and Fuchs reacted imidoyl chlorides (1 mol) (**327**) with diethyl sodiomalonate (1.4–2.5 mol) in diethyl ether in an autoclave at 80–150°C for 16–35 hr and obtained 2-aryl-4-hydroxyquinoline-3-carboxylates (**328**) in 26–38% yields (31M52).

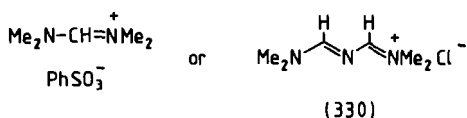


In a Vilsmeier–Haack–Arnold reaction, *N,N*-disubstituted aminomethylenemalonates (**329**) were prepared in good yields from the sodium derivative of diethyl malonate or from diethyl malonate in the presence of triethylamine in benzene or toluene at a temperature below 20°C with imidoyl chlorides, which were prepared *in situ* from *N,N*-disubstituted formamides and phosphoryl chloride (63BRP917436). Instead of diethyl malonate, diethyl ethoxymagnesiummalonate could also be used (63BRP917436).

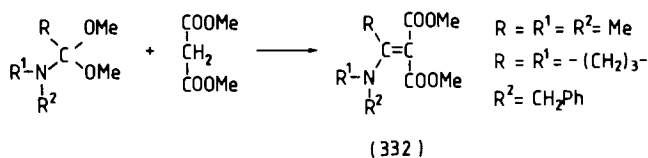
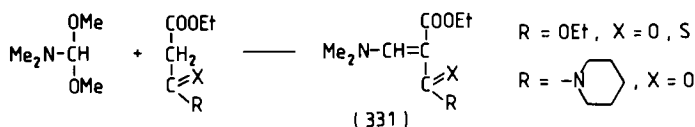


N,N-Dimethylaminomethylenemalonate (**329**, R = Me) was obtained in 81% yield from the reaction of diethyl malonate and its sodium derivative with DMF and phosgene in benzene at 60–70°C for 2 hr (61CB2278).

N,N-Dimethylaminomethylenemalonate (**329**, R = Me) was prepared in the reaction of diethyl malonate and DMF diethyl acetal at 130–150°C for 90 min (71S220), or in the reaction of the sodium salt of diethyl malonate and tetramethylformamidine benzenesulfonate in ethanol at ambient temperature for 20 hr (71S220), or in the reaction of diethyl malonate and Gold's reagent (**330**) in the presence of sodium ethylate in ethanol at reflux temperature overnight (82SC939), in 77%, 50%, and 74% yields, respectively.

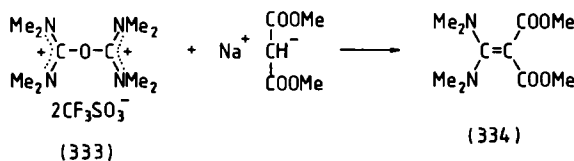


Dimethylformamide dimethyl acetal was reacted with malonic acid derivatives at room temperature for 6 hr (84TL3743) or at 110°C for 1–2 hr (780PP67) to afford *N,N*-dimethylaminomethylene derivatives (**331**) in 75–96% yields.



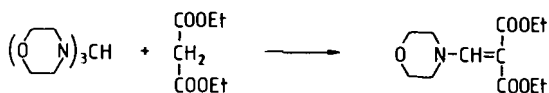
The reaction of *N,N*-dimethylacetamide dimethyl acetal and dimethyl malonate at ambient temperature for 1 week, and that of 1-benzyl-2-pyrrolidone dimethyl acetal and dimethyl malonate in boiling methanol for 36 hr, gave *N,N*-disubstituted aminomethylenemalonates (**332**) in 60% and 87% yields, respectively (69JA6683).

The reaction of bis(tetramethylformamidine)ether (**333**) and dimethyl sodiomalonate in acetonitrile at ambient temperature for 15 min afforded dimethyl bis(dimethylamino)methylenemalonate (**334**) in 55% yield (84SC1073). Bis(dimethylamino)methylenemalonate (**334**) was earlier obtained in 13% yield in the reaction of dimethyl sodiomalonate and *N,N,N',N'*-tetramethylmethylthioformamidine iodide in a mixture of dioxane and methylene chloride at ambient temperature for 0.5 hr and then at 50°C for 1 hr (70ACS102).



The mildly exothermic reaction of diethyl malonate and trimorpholinomethane in ethanol at 50°C afforded morpholinomethylenemalonate in 71% yield (80JOC3986) (Scheme 30).

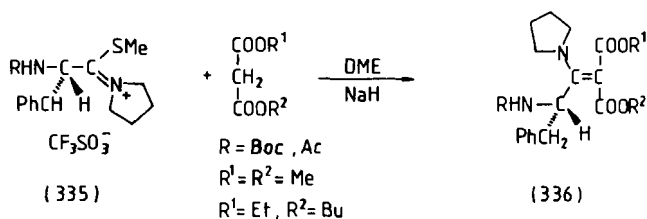
The reaction of 1,1-dimorpholinoethene and diethyl malonate in boiling



SCHEME 30

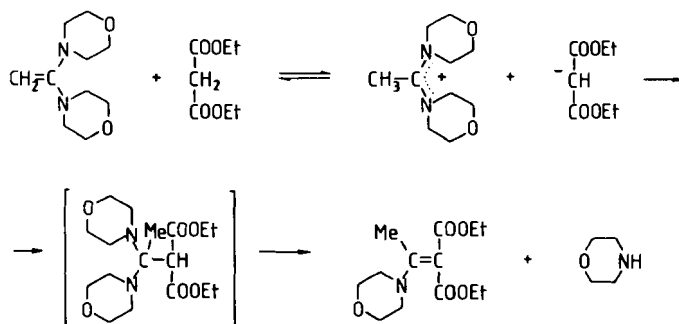
diethyl ether or THF for 8 hr gave diethyl 1-(4-morpholinyl)ethylidene-malonate in 10% yield (87CJC2717) (Scheme 31).

Thioiminium salts (**335**) were reacted with dialkyl malonates in the presence of sodium hydride in 1,2-dimethoxyethane (DME) to give dialkyl aminomethylenemalonates (**336**) in 21–43% yields (88TL2299).

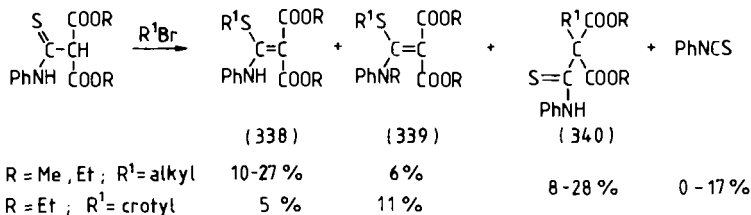
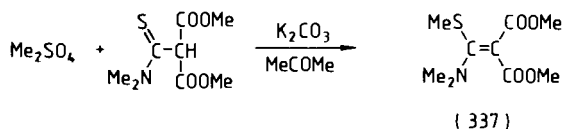


10. FROM DIALKYL 2-AMINOTHIACARBONYLMALONATES, DIALKYL (2-ALKYLTHIO)THIACARBONYL MALONATES AND THEIR DERIVATIVES

The reaction mixture of dimethyl *N,N*-dimethylaminothiocarbonylmalonate and dimethyl sulfate in the presence of potassium carbonate in acetone was boiled for 6 hr to give methylthio(dimethylamino)methylenemalonate (**337**) in 60% yield (69T4649).

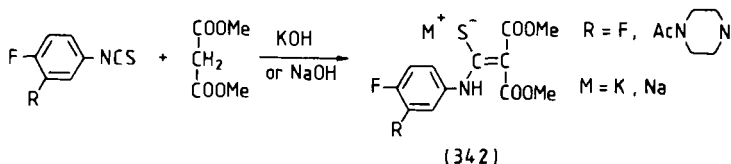
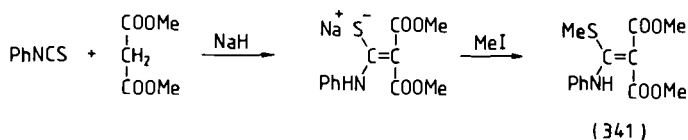


SCHEME 31



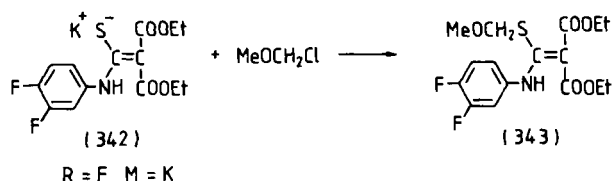
Dialkyl *N*-phenylaminothiocarbonylmalonates were reacted with alkyl bromides in DMF in the presence of sodium hydride at ambient temperature for 2 hr to give a mixture of products (338–340), which were separated by means of column chromatography. Dialkyl (alkylthio)(phenylamino)-methylenemalonates (338 and 339) were obtained in 5–27% yields (74T1283).

Dimethyl malonate was first treated dropwise with phenyl isothiocyanate in the presence of sodium hydride in *N,N*-dimethylacetamide at 0°C. The reaction mixture was stirred at ambient temperature for 1.5 hr and then cooled to 0°C, and methyl iodide was added dropwise. After stirring for 4 hr at room temperature, (methylthio)(phenylamino)methylenemalonate (341) was obtained in 79% yields (69T4649).



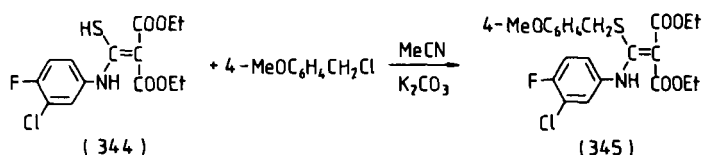
Diethyl malonate was reacted with (het)aryl isothiocyanates in the presence of potassium hydroxide or sodium hydride in dioxane or THF at

room temperature for 18 hr to give the alkali metal salts of (arylamino)mercaptomethylenemalonates (**342**) in good yields [84JAP(K)227887; 87BRP2190376].

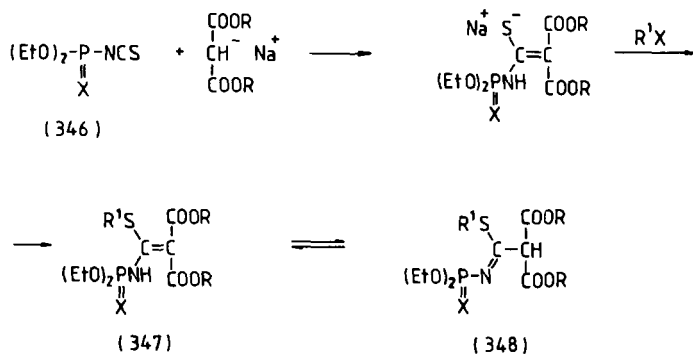


The potassium salt of (3,4-difluorophenylamino)mercaptomethylenemalonate (**342**, R = F, X = K) was reacted with methoxymethyl chloride in dioxane at room temperature for 3 hr to afford diethyl (3,4-difluorophenylamino)(methoxymethylthio)methylenemalonate (**343**) in good yield (87BRP2190376).

N-(3-Chloro-4-fluorophenyl)amino(mercapto)methylenemalonate (**344**) was reacted with 4-methoxybenzyl chloride in the presence of potassium carbonate in acetonitrile at ambient temperature for 3 hr to give *N*-(3-chloro-4-fluorophenyl)amino[(4-methoxybenzyl)thio]methylenemalonate (**345**) in 81% yield (82EUP58392).

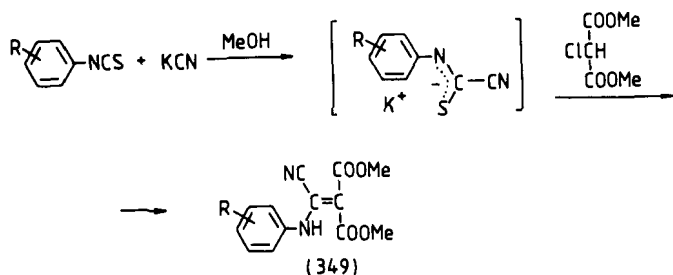


The sodium salts of dialkyl malonates were reacted with isothiocyanates (**346**) in diethyl ether or in THF at -10°C – 0°C . The products were then alkylated with alkyl halides to give mixtures of tautomeric (alkylthio)ami-



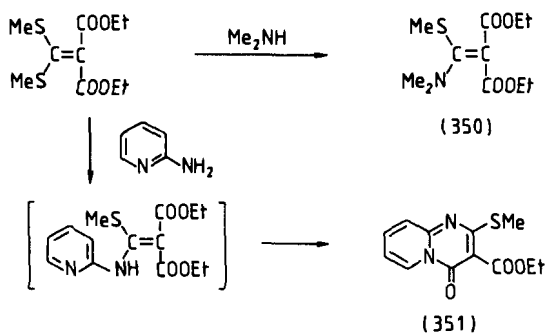
nomethylene- (347) and (alkylthio)iminomethylmalonates (348) in 52–76% yields (87ZOB772).

Dimethyl (arylamino)cyanomethylenemalonates (349) were prepared in 27–52% yields in the reactions of aryl isothiocyanates and potassium cyanide in methanol at room temperature for 45 min, followed by treatment with dimethyl chloromalonate for 3 hr (77S607).



Diethyl *N*-phenylaminothiocarbonylmalonate was reacted with hydrazine hydrate in boiling ethanol for 4 hr to give a mixture of 5-phenylamino-2-pyrazolin-5-one and monoethyl ester, a hydrazide of hydrazino(phenylamino)methylenepropanedioic acid (77G555).

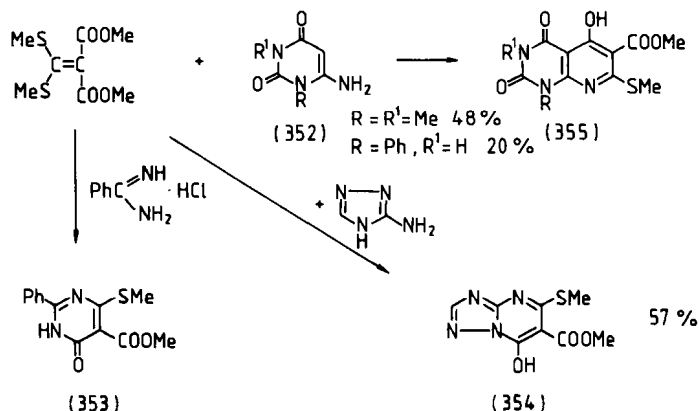
Diethyl bis(methylthio)methylenemalonate was reacted with dimethylamine in ethanol in a sealed tube at 120°C for 24 hr to give dimethyl (methylthio)(dimethylamino)methylenemalonate (350) 27% yield [78-ACS(B)421].



2-Aminopyridine was reacted with diethyl bis(methylthio)methylenemalonate at 150°C for 24 hr, then at 180°C for 6 h, to give 2-methylthiopyrido[1,2-*a*]pyrimidine-3-carboxylate (351) in 29% yield (88CP1232904).

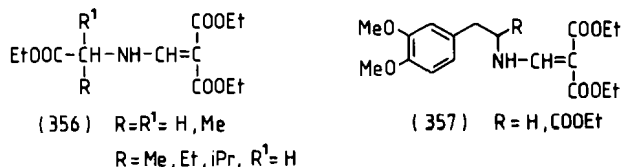
The reaction of dimethyl bis(methylthio)methylenemalonate and benzamidine hydrochloride in the presence of sodium methylate (83H1745), or in the presence of potassium carbonate in dimethylsulfoxide at 100°C for

10 hr (88JHC959), 3-amino-1,2,4-triazole in dimethylformamide at 150°C for 3 hr (85CPB962), and 6-aminouracils (**352**) in sulfolane at 150°C for 8 hr in the presence of potassium carbonate (84CPB122), gave pyrimidinone (**353**), 1,2,4-triazolo[1,5-*a*]pyrimidinecarboxylate (**354**), and pyrido[2,3-*d*]pyrimidinecarboxylates (**355**).



11. FROM DIETHYL 1,3-DIETHOXYCARBONYLGLUTACONATE AND ITS DERIVATIVES

Levy prepared monosubstituted aminomethylenemalonates (**356**) in the reactions of diethoxycarbonylglutaconate (**8**, $R = \text{H}$) and aminoester hydrochlorides in the presence of sodium ethylate in boiling ethanol (14JCS27).

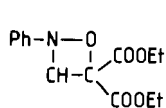


The reactions of 2-(3,4-dimethoxyphenyl)ethylamine hydrochlorides with the sodium derivative of diethoxycarbonylglutaconate (**8**, $R = \text{H}$) in refluxing ethanol afforded the corresponding aminomethylenemalonates (**357**) in 84–885 yields (56JOC336).

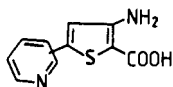
Diethyl aminomethylenemalonate (**13**) was prepared in the reaction of the ethoxycarbonyl derivative of diethoxycarbonylglutaconate (**8**, $R = \text{CH}_2\text{COOEt}$) and ammonia (02JPR1).

12. MISCELLANEOUS

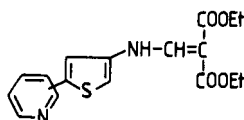
The exothermic reaction of nitrosobenzene and diethyl methylenemalonate in chloroform for a few minutes gave diethyl (*N*-hydroxy-*N*-phenylamino)methylenemalonate (**300**), but Ingold and Weaver described the structure of the reaction product as an oxazetidine derivative (**358**) (24JCS1456). This was questioned by Burkhardt and Lapwith (25JCS1748). They proposed a noncyclic structure (**300**), which was confirmed by Griffin *et al.* through the use of modern spectroscopic methods (63TL1365; 65T2735).



(358)



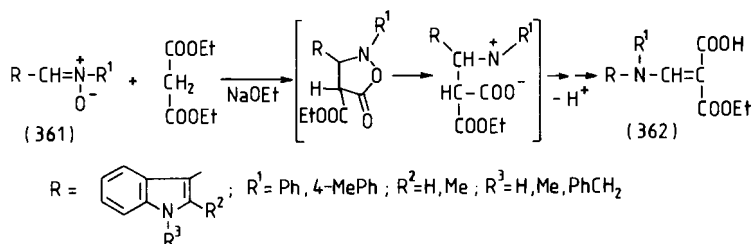
(359)



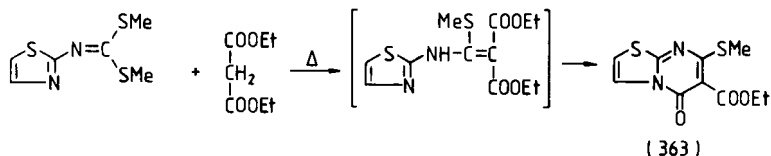
(360)

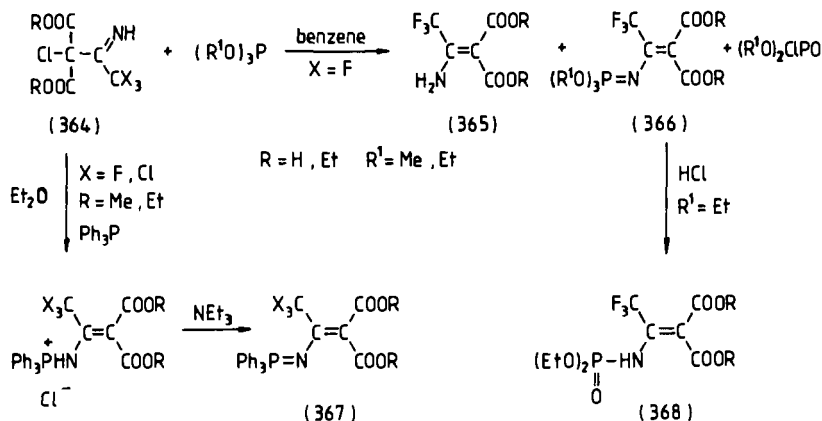
3-Amino-5-(pyridyl)thiophene-2-carboxylic acids (**359**) were reacted with diethyl methylenemalonate in DMF at 150°C for 2 hr to give *N*-[5-(pyridyl)thien-3-yl]aminomethylenemalonates (**360**) 61–62% yields [82-JAP(K)116077].

The rearrangement and subsequent reaction of nitrones (**361**) with diethyl malonate on the action of sodium ethylate in boiling benzene afforded monoethyl 3-indolylaminomethylenemalonates (**362**) in 17–72% yields (82ZOR2001; 83ZOR1518).



Thiazolo[3,2-*a*]pyrimidine-6-carboxylate (**363**) was prepared in 15% yield in the reaction of dimethyl 2-thiazolyldithiocarbonimidate and diethyl malonate at 140°C for 24 hr (88CP1232904).



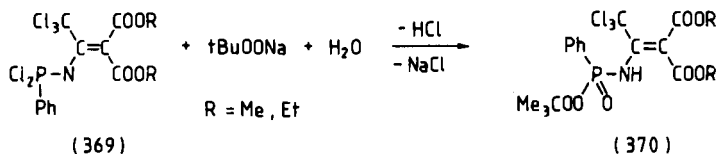


SCHEME 32

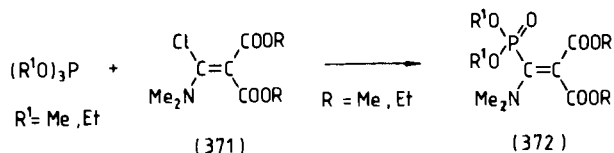
The electrochemical oxidation of diethyl *N,N*-bis(2,4,6-trimethoxyphenyl)aminomethylmalonate in acetonitrile in the presence of lithium perchlorate and 4-picoline gave *N,N*-bis(2,4,6-trimethoxyphenyl)aminomethylenemalonate in 76% yield (81M14).

When reacted with trialkyl phosphite in benzene for 1 hr, dialkyl malonates (364, X = F) gave a mixture of amino(trifluoromethyl)methylenemalonates (365) (20% yields), dialkyl trifluoromethyl(substituted amino)methylenemalonates (366) (40–45% yields), and dialkyl chlorophosphate (~20%) (86ZOB805). The reactions of dialkyl malonates (364, X = F, Cl) and triphenylphosphine in the presence of triethylamine in diethyl ether for 1 hr gave trihalomethyl(substituted amino)methylenemalonates (367) in 87–95% yields. The treatment of a solution of dialkyl trifluoromethyl(substituted amino)methylenemalonates (366, R¹ = Et) in benzene with aqueous hydrochloric acid gave amino(trifluoromethyl)methylenemalonates (368) in 82–84% yields (86ZOB805) (Scheme 32).

Dialkyl trichloromethyl(substituted amino)methylenemalonates (370) were prepared in 91–92% yields in the reactions of malonates (369) and sodium *tert*-butyl peroxide in aqueous ethanol at room temperature for 1–1.5 hr (83ZOB2152).



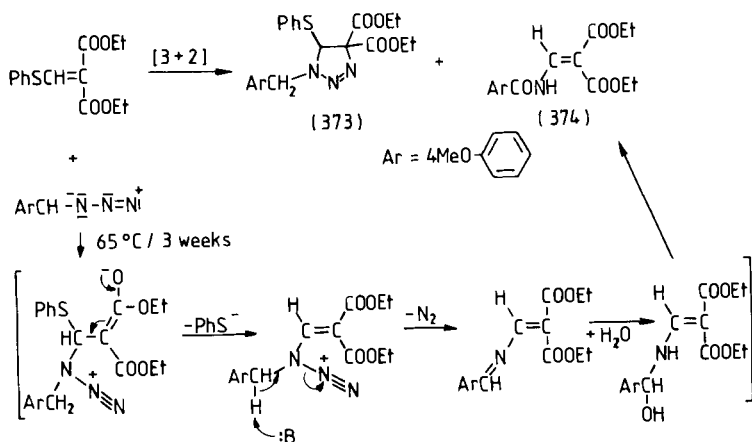
The reactions of dialkyl (dimethylamino)chloromethylenemalonates (**371**) and trialkyl phosphite afforded aminomethylenemalonates (**372**). Their insecticidal activities against aspid s and flies were investigated (84MI3).



Diethyl phenylthiomethylenemalonate was reacted with 4-methoxybenzyl azide at 65°C for 3 weeks. The reaction mixture was then treated with methanol, and the methanolic solution was stored at -20°C for 2 days to give 1,2,3-triazole (**373**) as crystals in 30% yield. A week later, the crystals of diethyl (4-methoxybenzoylamino)methylenemalonate (**374**) were also precipitated in 7% yield from the methanolic mother liquid (87CCC207) (Scheme 33). It was suggested that the triazine (**373**) was probably formed by an alternative mechanism.

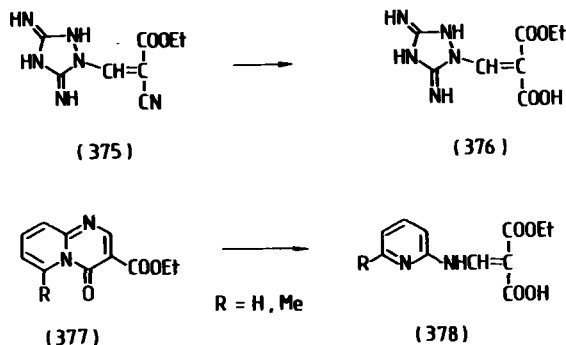
The hydrolysis of ethyl (1,2,4-triazol-3-ylmethylene)cyanoacetate (**375**) in aqueous hydrochloric acid gave monoethyl (1,2,4-triazol-3-yl)methylenemalonate (**376**) (57G931).

The treatment of 6-methyl-4-oxo-pyrido[1,2-*a*]pyrimidine-3-carboxylate (**377**, R = Me) with a 3-25-fold excess of alcohol in the presence



SCHEME 33

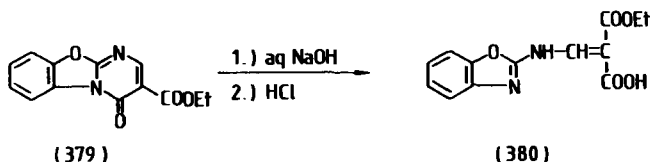
of a mineral acid or a Lewis acid catalyst at 75–80°C for 4 hr gave dialkyl *N*-(6-methyl-2-pyridyl)aminomethylenemalonates (**262**, R = Me, R' = alkyl) (84MIP1).



The hydrolysis of 4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxylates (**377**, R = H, Me) in water at ambient temperature for one week afforded 20% of monoethyl (2-pyridylamino)methylenemalonate (**378**, R = H), whereas the 6-methyl derivative (**378**, R = Me) was obtained in 76% yield after 1 day [72AF815; 74JCS(P1)1753].

Mild hydrolysis of ethyl 4-oxo-4*H*-pyrimido[1,2-*a*]pyridazine-3-carboxylate in 0.1 N sodium hydroxide solution at room temperature afforded monoethyl (3-pyridazinylamino)methylenemalonate (68TL33).

The hydrolysis of pyrimido[1,2-*b*]benzoxazole (**379**) with 1 mol. equiv. of 0.5% aqueous sodium hydroxide solution at 50°C for 40 min gave a ring-opened product (**380**) in 69% yield (79JOC1811).

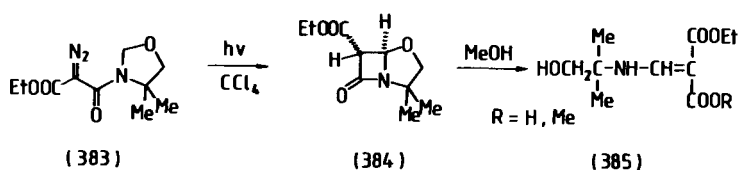


Pyrimido[1,2-*c*]quinoxaline (**381**) was treated dropwise with 1 N sodium ethoxide-ethanol solution in dimethyl sulfoxide (DMSO) at ambient temperature for 3 hr to give diethyl (4-quinoxalinylamino)methylenemalonate (**382**) in 39% yield (81EUP30156).

Methanolysis of 4-oxo-1-azabicyclo[3.2.0]heptane (**384**), obtained in the photoreaction of oxazolidine (**383**), gave ethylmethyl *N*-(2-hydroxy-

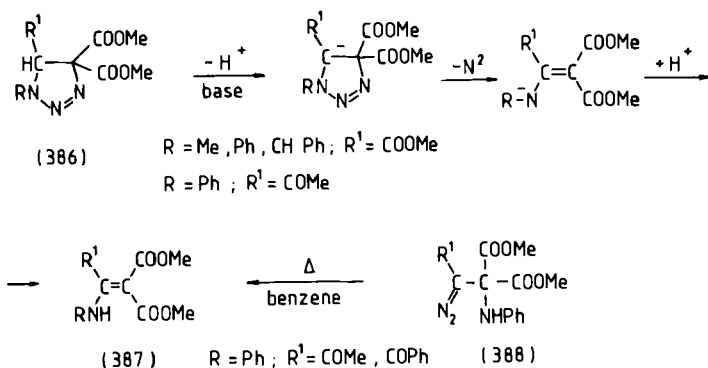


1,1-dimethylethyl)aminomethylenemalonate (**385**, R = Me) [73CC293; 75JCS(P1)1517]. This product (**385**, R = Me) was also prepared in the reaction of 2-amino-2-methylpropan-1-ol and ethylmethyl ethoxymethylenemalonate in dichloromethane [75JCS(P1)1517]. When 4-oxo-1-azabicyclo[3.2.0]heptane (**384**) was chromatographed on silica gel, monoethyl *N*-(2-hydroxy-1,1-dimethylethyl)aminomethylenemalonate (**385**, R = H) was obtained [73CC293; 75JCS(P1)1517].



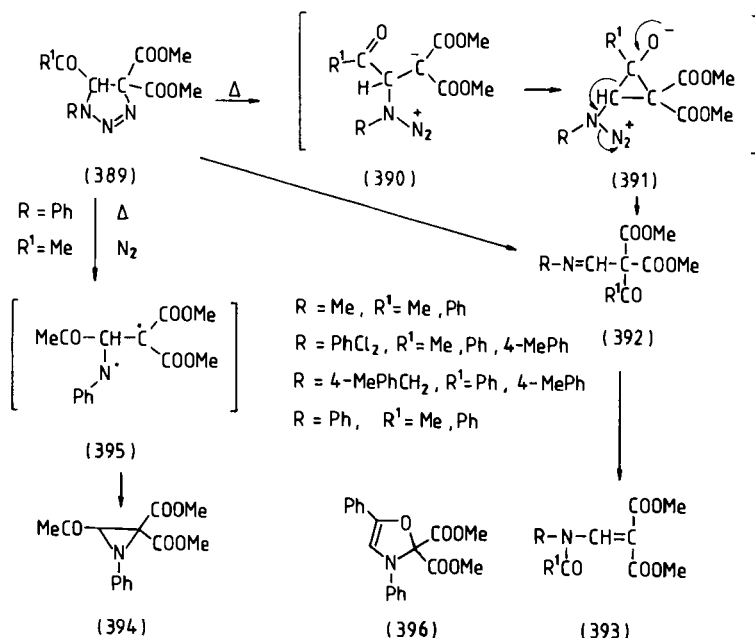
1,2,3-Triazoles (**386**, R¹ = COOMe) were treated with potassium *tert*-butylate in a mixture of *tert*-butanol and benzene for 15–60 min to give (substituted amino)methoxycarbonylmethylenemalonates (**387**, R¹ = COOMe) in 28–54% yields. In the case of the acetyl derivative (**386**, R = Ph, R¹ = COMe), the reaction was carried out in chloroform in the presence of triethylamine at ambient temperature for 8 hr. to give (phenylamino)acetylmethylenemalonate (**387**, R = Ph, R¹ = COMe) in 38% yield. (Phenylamino)acylmethylenemalonates (**387**, R = Ph, R¹ = COMe, CPh) were also prepared in 62–74% yields when diazo derivatives (**388**, R¹ = COMe, CPh) were heated in benzene for 4–24 hr (80T1821) (Scheme 34).

The thermolysis of 5-acyl-1,2,3-triazolines (**389**) in boiling toluene under nitrogen for 16–68 hr afforded acylaminomethylenemalonates (**393**) in 18–84% yields (85BSF809). It was suggested that in the first step of the thermolysis, imines (**392**) were formed, probably via the zwitterions **390** and **391** by the loss of nitrogen and a 1,2-acyl shift, or directly by a concerted process from 5-acyltriazolines (**389**). Then acylaminomethylenemalonates (**393**) might form from imines (**392**) by 1,3-migration of the acyl group (Scheme 35).

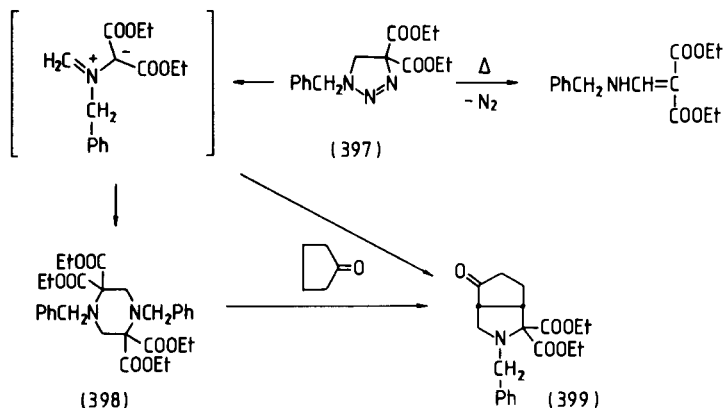


SCHEME 34

The thermolysis of 5-acetyl-1-phenyltriazoline (**389**, $\text{R} = \text{Ph}$, $\text{R}^1 = \text{Me}$) in boiling benzene or toluene for 24 hr gave a mixture of acylaminomethylenemalonate (**393**, $\text{R} = \text{Ph}$, $\text{R}^1 = \text{Me}$), aziridine (**394**), and imine (**392**, $\text{R} = \text{Ph}$, $\text{R}^1 = \text{Me}$). The aziridine (**394**) might be formed from a 1,3-biradical (**395**). Whereas the imine (**392**, $\text{R} = \text{Ph}$, $\text{R}^1 = \text{Me}$) rearranged in



SCHEME 35

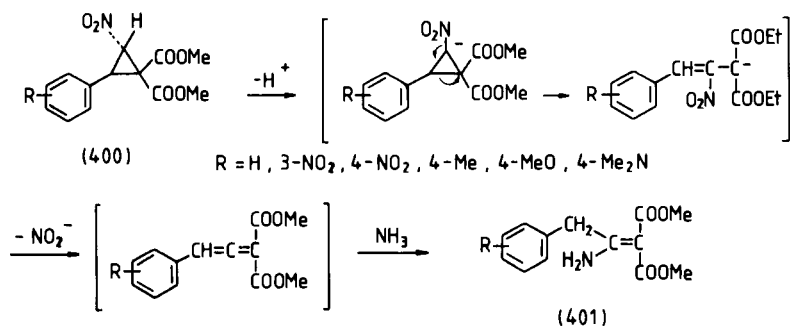


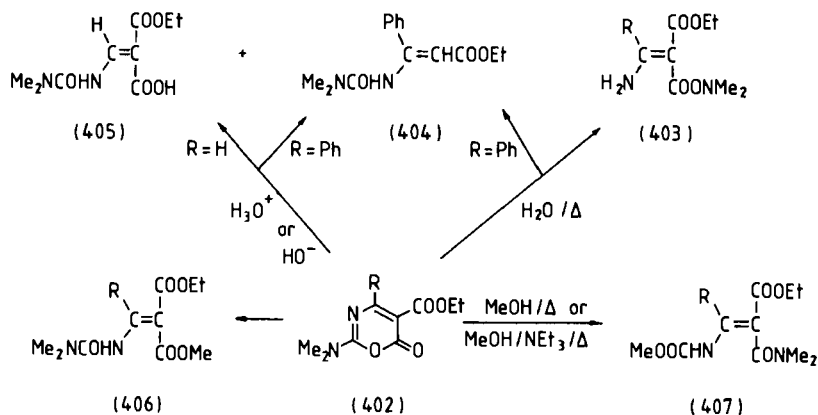
SCHEME 36

boiling toluene to acylaminomethylenemalonate (**393**, $R = Ph$, $R^1 = Me$), the aziridine (**394**) did not. The thermolysis of 5-benzoyl-1-phenyltriazoline (**389**, $R = R^1 = Ph$) in boiling benzene led to the formation of a mixture of *N*-benzoylaminomethylenemalonate (**393**, $R = R^1 = Ph$), imine (**392**, $R = R^1 = Ph$), and 4-oxazoline (**396**) (85BSF809).

1,2,3-Triazoline-4,4-dicarboxylate (**397**) was reacted with cyclopentanone in boiling toluene overnight under nitrogen. From the reaction mixture, diethyl *N*-benzylaminomethylenemalonate, tetraethyl 1,4-dibenzylpiperazinetracarboxylate (**398**), and a bicyclic product (**399**) were isolated by preparative thin-layer chromatography in 29%, 4%, and 68% yields, respectively [84JCS(P1)2517] (Scheme 36).

The reaction of dimethyl cyclopropanedicarboxylates (**400**) and ammonia in methanol at $0^\circ C$ gave dimethyl amino(benzyl)methylenemalonates (**401**) in 20–80% yields (75ZOR68).

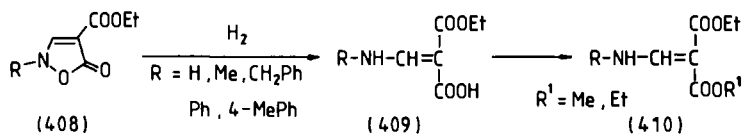




SCHEME 37

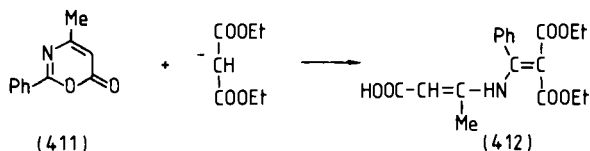
The reactions of 1,3-oxazinones (402, $\text{R} = \text{H}, \text{Ph}$) and water in boiling dioxane for 0.5 and 2 hr gave aminomethylenemalonamate (403, $\text{R} = \text{H}$) in 85% yield, when $\text{R} = \text{H}$, and a mixture of amino(phenyl)methylenemalonamate (403, $\text{R} = \text{Ph}$) and 3-(substituted amino)-3-phenylacrylate (404) in 59% and 33% yields, respectively, when $\text{R} = \text{Ph}$. The alkaline hydrolysis of 1,3-oxazinones (402) with aqueous sodium hydroxide solution in dioxane at ambient temperature for 20 min afforded monoethyl *N*-(dimethylaminocarbonyl)aminomethylenemalonate (405) in 24% yield, when $\text{R} = \text{H}$, and the acrylate (404) in 27% yield when $\text{R} = \text{Ph}$. The methanolysis of 1,3-oxazinone (402, $\text{R} = \text{H}$) in boiling methanol for 30 min gave ethylmethyl *N*-(dimethylaminocarbonyl)aminomethylenemalonate (406, $\text{R} = \text{H}$) in 75% yield, while in the presence of triethylamine in boiling methanol for 2.5 hr, a malonamate (407, $\text{R} = \text{H}$) was obtained in 81% yield. The 4-phenyl-1,3-oxazinone (402, $\text{R} = \text{Ph}$) afforded a mixture of malonamate (407, $\text{R} = \text{Ph}$) and ethylmethyl *N*-(dimethylaminocarbonyl)aminomethylenemalonate (406, $\text{R} = \text{Ph}$), with predominance of the latter under both conditions (87JOC3426) (Scheme 37).

The catalytic hydrogenation of isoxazolones (408) over 10% Pd—C or Raney—nickel catalysts in ethanol gave the half-esters of aminomethylenemalonates (409) in good yields (74G715). The half-esters (409) were

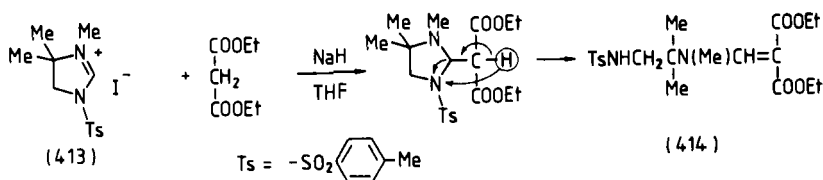


reacted with diazomethane and diazoethane in diethyl ether at ambient temperature to afford aminomethylenemalonates (**410**).

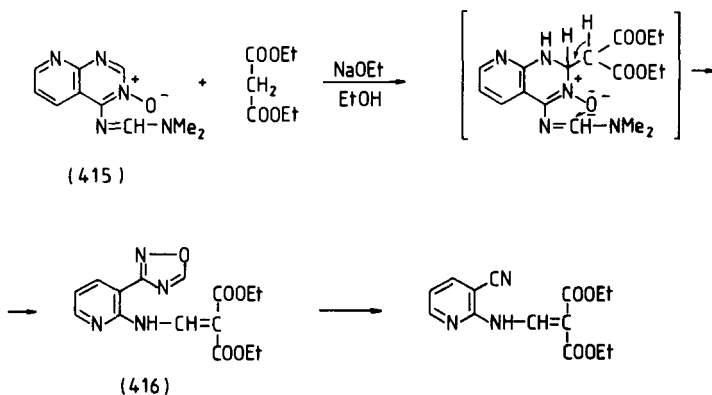
1,3-Oxazinone (**411**) was reacted with the carbanion of diethyl malonate to give (substituted amino)phenylmethylenemalonate (**412**) (86MI1).



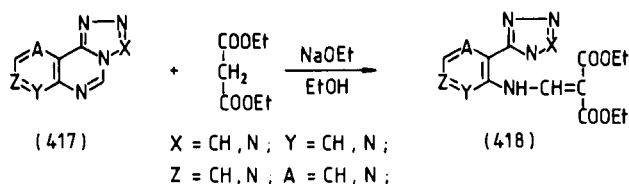
The reaction of an imidazolinium salt (**413**) and diethyl malonate in THF in the presence of sodium hydride at room temperature gave the aminomethylenemalonate derivative (**414**) in 65% and 82% yields (79CC117; 83T3971).



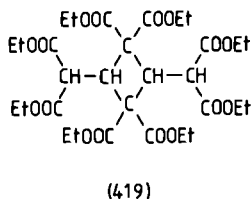
The reaction of pyrido[2,3-*d*]pyrimidine-3-oxide (**415**) and diethyl malonate in the presence of sodium ethylate in ethanol at 0°C for 10 min led to the formation of *N*-[3-(1,2,4-oxadiazol-3-yl)-2-pyridyl]aminomethylenemalonate (**416**) in 73% yield, but at ambient temperature for 1.5 hr, the product was diethyl *N*-(3-cyano-2-pyridyl)aminomethylenemalonate in 61% yield (83JOC4132).



Tricyclic pyrimidines (**417**) were reacted with diethyl malonate in ethanol in the presence of sodium ethylate at room temperature for 0.25–1.5 hr ($X = N$) or 12 hr ($X = CH$) to give ring-opened products (**418**) in 30–88% yields (83JOC4132; 85M1309).



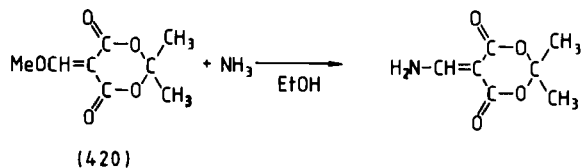
Diethyl aminomethylenemalonate (**13**) was obtained in the reaction of cyclobutanetetracarboxylate (**419**) and ammonia (09JPR393).



B. Syntheses of Alkylidene (1-Aminoalkylidene)malonates

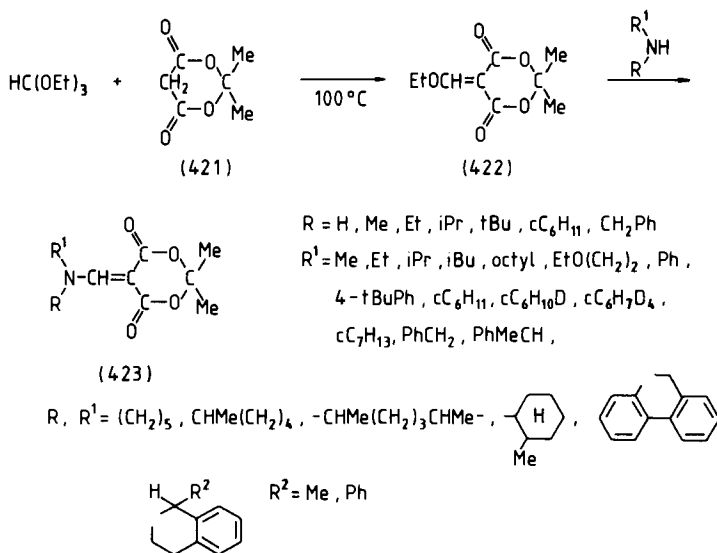
1. FROM ALKYLIDENE 1-ALKOXYALKYLIDENEMALONATES

Isopropylidene aminomethylenemalonate was prepared in 55% yield in the reaction of isopropylidene methoxymethylenemalonate (**420**) and ammonia in ethanol at ambient temperature for 12 hr (67M564). Wentrup *et al.* obtained isopropylidene aminomethylenemalonate similarly (88JA-1337).



Meldrum's acid (**421**) was reacted with an excess of ethyl orthoformate by heating on a water-bath for 2 hr. A two-fold excess of the appropriate

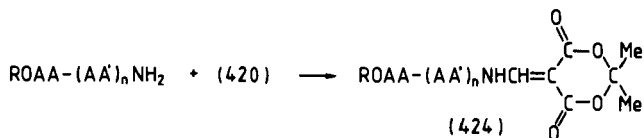
amine was then added to the reaction mixture, and heating was maintained for another 2 hr to give isopropylidene aminomethylenemalonates (**423**) in 11–90% yields [67M564; 84HCA1402, 84JCS(P1)2129; 86JCS(P1)1465; 87ABC2775, 87T4803; 88JA1880, 88JCS(P1)863, 88JCS(P1)869]. When ethylamine was applied, the reaction was carried out in an autoclave at 80–90°C for 2 hr, and isopropylidene *N*-ethylaminomethylenemalonate (**423**, R = H, R¹ = Et) was obtained in 35% yield.



Isopropylidene methoxymethylenemalonate (**420**) was reacted with amines in boiling cyclohexane for 24 hr, or in acetonitrile at 20°C for 5–30 min, to give aminomethylenemalonates (**423**) in 40–99% yields [86JCS(P1)1465; 88JCS(P1)863, 88JCS(P1)869].

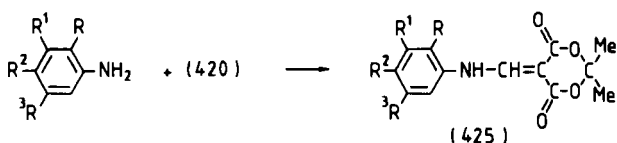
1-Amino-1-deoxy-D-fructose acetate was reacted with isopropylidene methoxymethylenemalonate (**420**) in the presence of triethylamine in boiling methanol for 0.5 hr to afford aminomethylenemalonate (**19**) in 92% yield (86M110). The aminomethylenemalonate is present in several isomeric forms (**20–23**) in the solid state and in solution (see Scheme 5 and Table IV in Chapter III).

Isopropylidene methoxymethylenemalonate (**420**) was reacted with amino esters, amino acids, and dipeptides at 95–100°C to give rise to the corresponding isopropylidene aminomethylenemalonates (**424**) in 54–85% yields (85M13; 86YZ154).



AA = amino acid, $n = 0$; AA = Gly, Phe, Ala, Leu, Cys
 $n = 0$; R = H; AA = Gly, Phe, Ala
 $n = 1$; R = Et; AA-AA' = Phe-Leu
 $n = 1$; R = H; AA-AA' = Gly-Gly

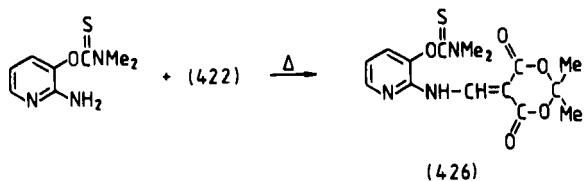
The reactions of isopropylidene methoxymethylenemalonate (**420**) and anilines at reflux temperature for 3–7 hr gave arylaminomethylenemalonates (**425**) in 62–92% yields (85SC125; 87T4803).



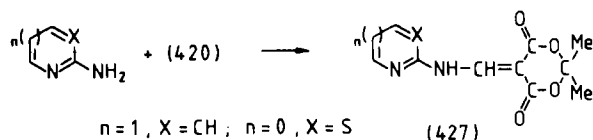
R = H, OMe, NO₂, R¹ = H, R² = H, Me, OMe, NO₂, Ac, R³ = H, OMe
R = R¹ = OMe, R² = H, R³ = CH₂NO₂, CH₂NHCO-CH₂Ph
R = R¹ = OMe, R² = H, R³ = CH(CN)OSiMe₂Bu

N-Ethyl-3-(4-pyridyl)aniline was reacted with isopropylidene ethoxymethylenemalonate (**422**) in ethanol at ambient temperature for about 15 hr to give isopropylidene *N*-ethyl-*N*-[3-(4-pyridyl)phenyl]aminomethylenemalonate in 72% yield [77JAP(K)116460].

2-Amino-3-[(dimethylamino)thiocarbonyloxy]pyridine was reacted with isopropylidene ethoxymethylenemalonate (**422**) under reflux for 2 hr to give isopropylidene 2-pyridylaminomethylenemalonate (**426**) in 44% yield (86EUP218423).

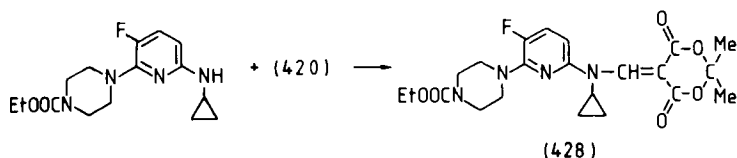


2-Aminopyridine and 2-aminothiazole were reacted with isopropylidene methoxymethylenemalonate under reflux to afford the corresponding 2-hetarylaminothiazolomethylenemalonates (**427**) in good yields (85SC125).

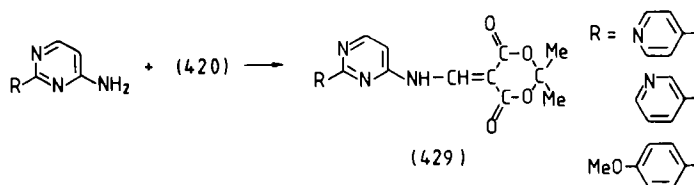


Isopropylidene *N*-(3-benzyloxy-2-pyridyl)- and *N*-(5-benzyloxy-4-pyrimidinyl)aminomethylenemalonates were prepared in the reactions of isopropylidene methoxymethylenemalonate (420) with 3-benzyloxy-2-aminopyridine or 5-benzyloxy-4-aminopyrimidine (89TL1529).

2-(Cyclopropylamino)-5-fluoro-6-(4-ethoxycarbonyl-1-piperazinyl)-pyridine was reacted with isopropylidene methoxymethylenemalonate (420) in methanol at ambient temperature for 4 hr to give isopropylidene 2-pyridylaminomethylenemalonate (428) in 67% yield (85EUP153163, 85EUP153828, 85EUP159174; 86EUP172651; 88EUP265230).



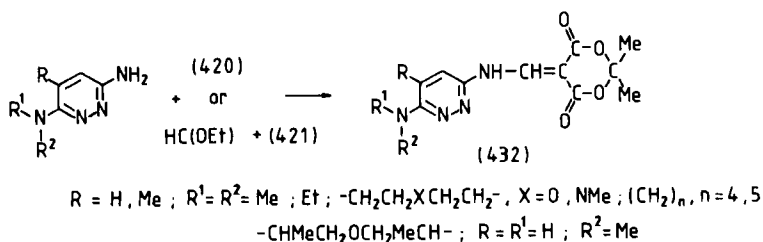
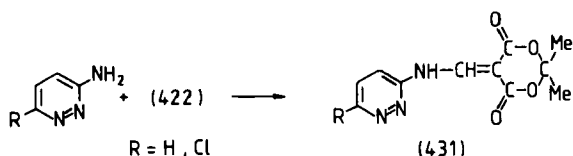
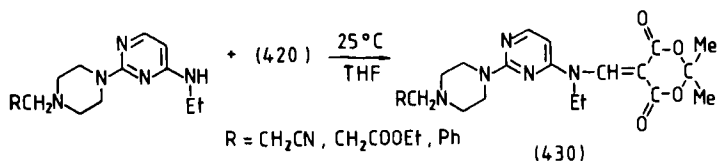
2-Substituted 4-aminopyrimidines were reacted with isopropylidene alkoxymethylenemalonates in boiling methanol for 30 min to give isopropylidene (4-pyrimidinylamino)methylenemalonates (429) in good yields (82JMC837; 84USP4432981).



The reactions of 4-(ethylamino)-2-(4-substituted piperazin-1-yl)pyrimidines and isopropylidene methoxymethylenemalonate (420) in THF at 25°C for 20 hr yielded *N*-ethyl-*N*-(4-pyrimidinyl)aminomethylenemalonates (430) in 71–82% yields [81JAP(K)99480, 81JAP(K)103178; 83JAP(K)-46084].

3-Aminopyridazine and its 6-chloro derivative were reacted with isopropylidene ethoxymethylenemalonates (422) at room temperature for 20 hr,

then at 80°C for 30 min to give (3-pyridazinylamino)methylenemalonates (**431**) in 79–81% yields (83H2225).



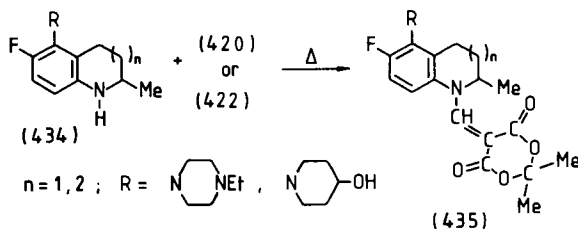
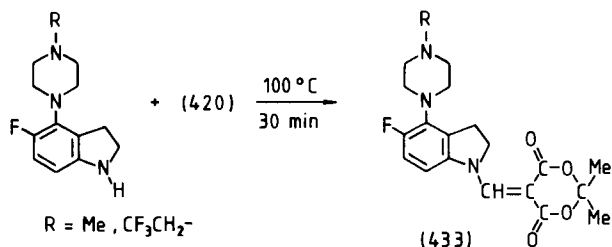
Isopropylidene 3-pyridazinylaminomethylenemalonates (**432**) were prepared in good yields in the reactions of 3-aminopyridazines and isopropylidene methoxymethylenemalonate (**420**) in alcohol, or in the reactions of 3-aminopyridazines, ethyl orthoformate, and Meldrum's acid (**421**) in ethanol (78GEP2737542, 78USP4104385).

The reaction of 2-aminoquinoxaline and isopropylidene methoxymethylenemalonate (**420**) in methanol afforded isopropylidene 2-quinoxalinyllaminomethylenemalonate (83EUP86723).

4-Aminoquinazoline was reacted with isopropylidene ethoxymethylenemalonate (**422**) in DMF at ambient temperature for 1 hr, then at 110°C for 10 min to give isopropylidene 4-quinazolinylaminomethylenemalonate in 69% yield (81EUP30156).

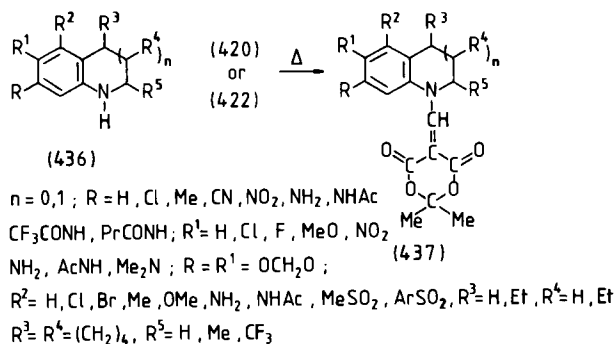
Indolines were reacted with isopropylidene methoxymethylenemalonate (**420**) at 100°C for 30 min to afford isopropylidene 1-indolinyllaminomethylenemalonates (**433**) in good yields (82BEP891046, 82BEP891537).

Isopropylidene alkoxyethylenemalonates were reacted with cyclic



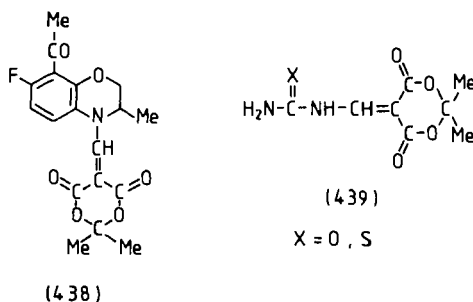
amines (434) at 160°C for 30 min to give aminomethylenemalonates (435) in 90–91% yields [83JAP(K)90511].

Bi- and tricyclic amines (436) were reacted with isopropylidene alkoxy-methylenemalonates at 110–120°C for 5 min to afford isopropylidene aminomethylenemalonates (437) in good yields [82JAP(K)2285, 82JAP-(K)16882].



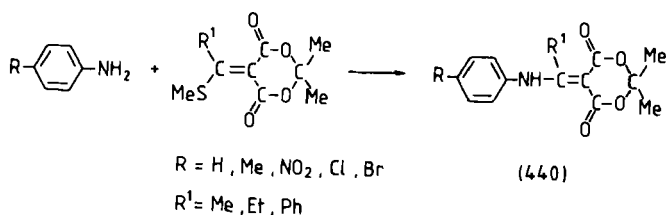
8-Acetyl-7-fluoro-3-methyl-1,4-benzoxazine was reacted with isopropylidene alkoxy-methylenemalonates in methanol at room temperature for

18–24 hr to give *N*-(1,4-benzoxazin-4-yl)aminomethylenemalonates (**438**) in 68–82% yields (84EUP106489; 85EUP153163; 87JHC1509).



Isopropylidene methoxymethylenemalonate (**420**), prepared from Meldrum's acid (**421**) and methyl orthoformate, was reacted with urea and thiourea under reflux for 2 hr to give aminomethylenemalonates (**439**) in 82% and 72% yields, respectively (84SC961).

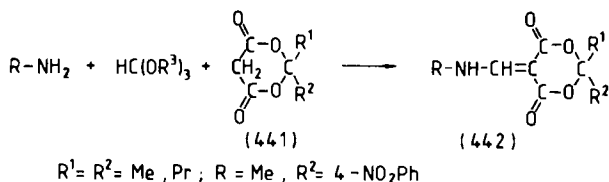
The reactions of isopropylidene (1-methylthioalkylidene)malonates and arylamines in boiling ethanol for 2–4 hr, or in diphenyl ether at 140°C for 0.5 hr, afforded isopropylidene 1-(arylamino)alkylidenemalonates (**440**) in 54–87% yields (87S482).



2. ONE-POT SYNTHESSES

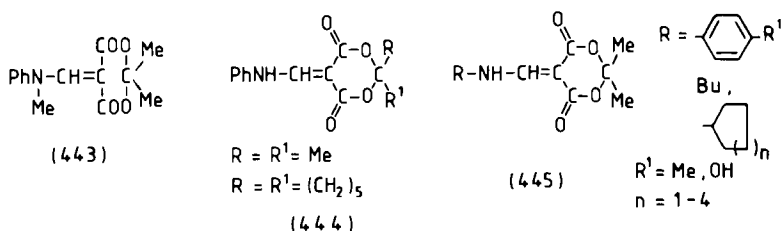
Because of the higher CH acidity (by 7–8 pK_a units) of alkylidene malonates (**441**), as compared with that of dialkyl malonates (87JA809), “one-pot” syntheses of alkylidene aminomethylenemalonates (**442**) could be carried out readily with a wide variety of primary and secondary aliphatic and cycloaliphatic amines, anilines, naphthylamines and heterocyclic amines, trialkyl orthoformate, and alkylidene malonates (83MI1; 86MI9). It was proposed that the higher CH acidity of alkylidene malonates was a consequence of the electrostatic (dipole–dipole) repulsion effects

arising in the fixed *anti* conformation of the ester groups of alkylidene malonates (88JA1870, 88JA1872).



Anilines, bis(2-amino-4-chlorophenyl)disulfide, naphthylamine, 2- and 3-aminopyridines, 2-aminopyrimidines, 2-, 3-, 5-, 6-, 7-, and 8-aminoquinolines, 6-aminocoumarin, and 2-aminopyrazine were reacted in the absence or presence of a solvent (ethanol, toluene) with ethyl orthoformate and isopropylidene or 4-heptylidene malonates to give alkylidene (het)arylaminomethylenemalonates (**442**, $\text{R}^1 = \text{R}^2 = \text{Me, Pr}$) in 32–100% yields [69BRP1147759; 75USP3907798; 88JAP(K)239269]. *p*-Toluenesulfonic acid monohydrate was sometimes applied as catalyst.

In the reaction of *N*-methylaniline, ethyl orthoformate, and Meldrum's acid (**421**) in the presence of *p*-toluenesulfonic acid monohydrate at 100°C for 2 hr, then for 3 days at ambient temperature, (*N*-methyl-*N*-phenylamino)methylenemalonate (**443**) was obtained in 41% yield (69BRP1147759).

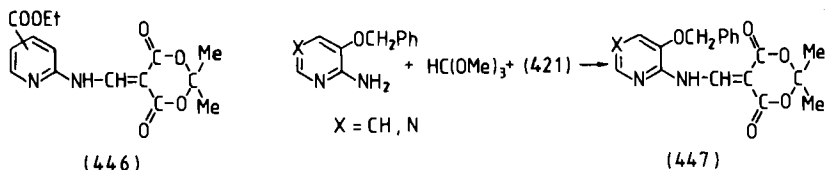


Phenylaminomethylenemalonates (**444**) were prepared in 92–95% yields in the reactions of aniline, ethyl orthoformate, and the appropriate cyclic ester of malonic acid [**441**, $\text{R} = \text{R}^1 = \text{Me, } -(\text{CH}_2)_5-$] at reflux temperature or 15 min (80CB2630).

The reactions of 4,6-dioxo-2-methyl-2-(4-nitrophenyl)-1,3-dioxane (**441**, $\text{R}^1 = \text{Me, R}^2 = 4\text{-NO}_2\text{Ph}$), ethyl orthoformate, and anilines in boiling acetic acid for 5 min gave arylaminomethylenemalonates (**442**, $\text{R} = \text{aryl, R}^1 = \text{Me, R}^2 = 4\text{-NO}_2\text{Ph}$) in 65–70% yields [78ZN(B)1550].

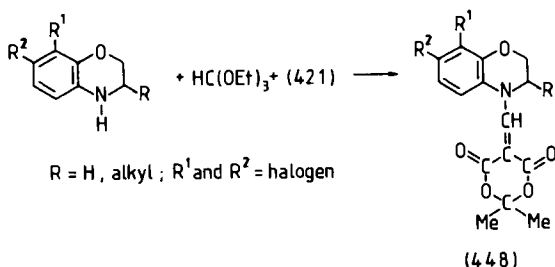
Amines were reacted with Meldrum's acid (**421**) and ethyl orthoformate at 5–80°C for 15–60 min to afford isopropylidene aminomethylenemalonates (**445**) in 21–86% yields [84JOC2772].

Isopropylidene *N*-(ethoxycarbonyl-2-pyridyl)aminomethylenemalonates (**446**) were prepared in 66–88% yields in the reactions of Meldrum's acid (**421**), ethyl 2-aminopyridinecarboxylates, and ethyl orthoformate in the presence of zinc chloride catalyst at 100–120°C for 15 min (78M15).



2-Amino-3-benzyloxypyridine (X = CH) and 4-amino-5-benzyloxypyrimidine (X = N) were reacted with Meldrum's acid (**421**) and methyl orthoformate in the presence of zinc chloride to give (hetarylamino)methylene-malonates (**447**) (89TL1529).

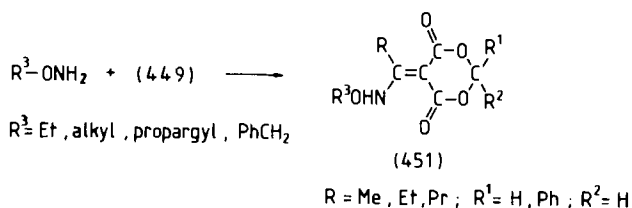
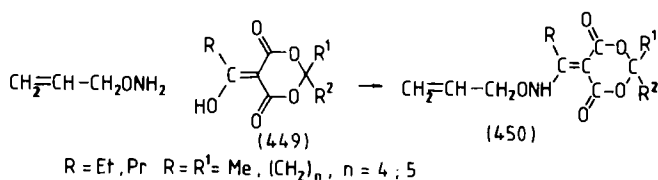
1,4-Benzoxazines were reacted with Meldrum's acid (**421**) and ethyl orthoformate in refluxing toluene for 1.5 hr to give (1,4-benzoxazin-4-yl)methylenemalonates (**448**) in good yields [83JAP(K)198405].



Isopropylidene (7,8-difluoro-3-methyl-1,4-benzoxazin-4-yl)methylene-malonate (**448**, R = Me, R¹ = R² = F) was prepared in 81% yield in the reaction of 7,8-difluoro-3-methyl-1,4-benzoxazine, ethyl orthoformate, and Meldrum's acid (**421**) at 110–120°C [84JAP(K)122493, 84JAP(K)-216890].

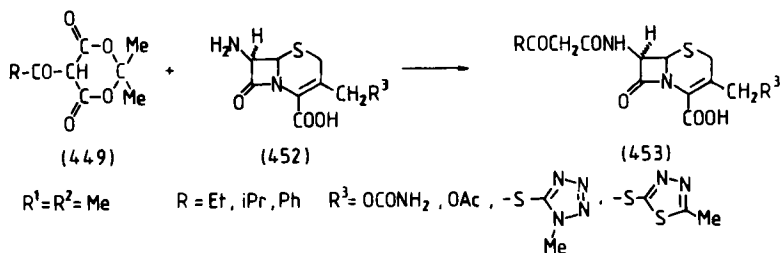
3. MISCELLANEOUS

The reactions of 4-hydroxy-5-acyl-1,3-dioxan-6-ones (**449**) and (allyloxy)amine in ethanol at 40°C for 10–60 min afforded 1-(allyloxyamino)alkylidenemalonates (**450**) (75GEP2524577).



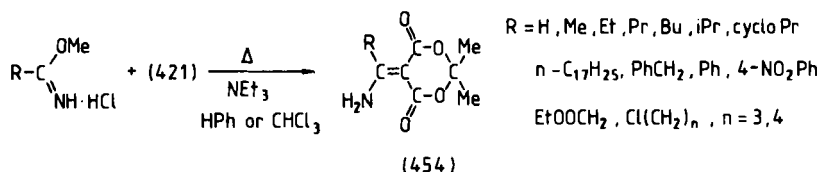
Alkylidene 5-acylmalonates were reacted with *O*-substituted hydroxylamine to give aminomethylenemalonates (**451**) [82JAP(K)62274].

However, when 7β-amino-ceph-3-em-4-carboxylic acids (**452**) were first reacted with *N,O*-bis(trimethylsilyl)acetamide in THF and then with isopropylidene 5-acylmalonate (**449**, R¹ = R² = Me), instead of the corresponding aminomethylenemalonate, 7β-acylamido-ceph-3-em-4-carboxylic acids (**453**) were obtained (83EUP54970).

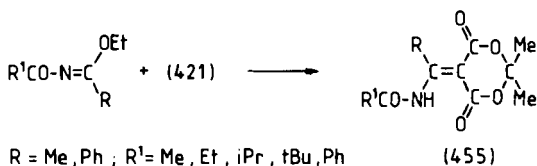


Isopropylidene malonate (**421**) was reacted with imidate hydrochlorides in the presence of triethylamine in chloroform or benzene under reflux

overnight to give isopropylidene (1-aminoalkylidene)malonates (**454**) in 7–92% yields (81S130; 88JA1337).



Meldrum's acid (**421**) was reacted with *N*-acylimidates in boiling chloroform in the presence of a few drops of triethylamine for 18 hr to give isopropylidene acylaminomethylenemalonates (**455**) in 67–86% yields (86CPB1980). Acylaminomethylenemalonates (**455**) could not be prepared from the corresponding isopropylidene aminomethylenemalonate by acylation.

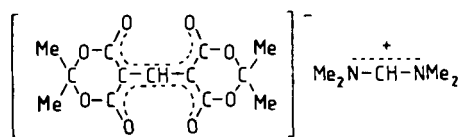


Isopropylidene phenylaminomethylenemalonate (**440**, $\text{R} = \text{R}^1 = \text{H}$) was prepared in 66% yield in the reaction of Meldrum's acid (**421**) and *N,N'*-diphenylformamidine in boiling benzene for 5 hr (67M564).

The treatment of Meldrum's acid (**421**) with DMF diethyl acetal in methanol for 3–5 hr (80CB2545) or in a mixture of diethyl ether and acetone for 1 hr (88KGS184) at ambient temperature gave isopropylidene *N,N*-dimethylaminomethylenemalonate (**423**, $\text{R} = \text{R}^1 = \text{Me}$).

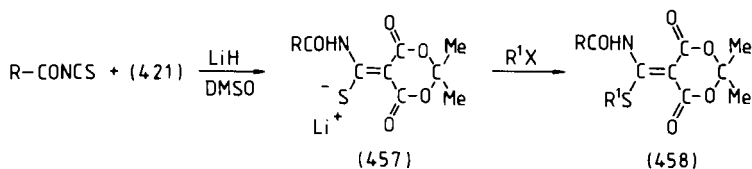
Isopropylidene *N,N*-dimethylaminomethylenemalonate (**423**, $\text{R} = \text{R}^1 = \text{Me}$) was prepared in 77% yield when a solution of Meldrum's acid (**421**) in THF was added dropwise to a solution of DMF dimethyl acetal in THF over a period of 1 hr at 0–5°C in the presence of sodium methylate. The reaction mixture was then stirred for 17 hr (80SC661).

Isopropylidene benzylaminomethylenemalonate was obtained in the reaction of isopropylidene *N,N*-dimethylaminomethylenemalonate (**423**, $\text{R} = \text{R}^1 = \text{Me}$) and benzylamine in ethanol at room temperature for 90 min, or in the reaction of **456** and benzylamine in ethanol in the presence of catalytic amount of acetic acid at ambient for 3 hr, in 90% and 83% yields, respectively (88KGS184).



(456)

The reactions of Meldrum's acid (**421**) and acyl isothiocyanates in DMSO in the presence of lithium hydride at ambient temperature for 2–3 hr gave the lithium salts (**457**), which were alkylated by treatment with alkyl halide for 5 hr to afford isopropylidene (acylamino)(alkylthio)methylenemalonates (**458**) in 20–90% yields (87ZC68).

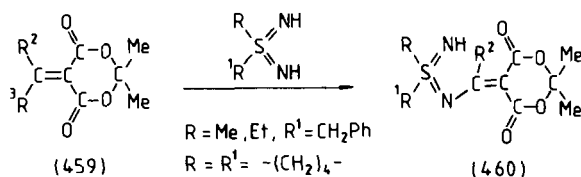


(457)

(458)

R = EtO, Ph, 2-ClPh, 2-BrPh, R¹ = Me, PhCH₂

The reactions of *S,S*-dialkylsulfur diimides and isopropylidene ethoxy-methylenemalonate (**459**, R² = H, R³ = OEt) or in isopropylidene bis-(methylthio)methylenemalonate (**459**, R² = R³ = SMe) in boiling methy-

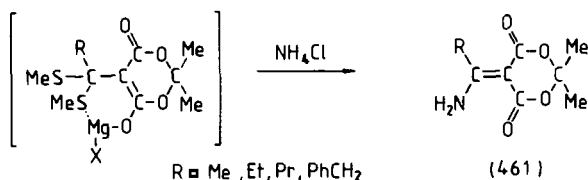


(459)

(460)

R² = R³ = SMeR² = H, R³ = OEt

rt.
THF

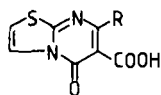
R = Me, Et, R¹ = CH₂PhR = R¹ = -(CH₂)₄-R² = H, MeSR = Me, Et, Pr, PhCH₂

(461)

lene chloride gave the corresponding aminomethylenemalonates (**460**) in 53–85% yields (88CB805).

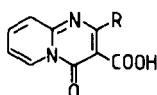
Isopropylidene bis(methylthio)methylenemalonate (**459**, $R^2 = R^3 = \text{SMe}$) was reacted with Grignard reagents in THF at room temperature for 1 hr and then with 10% aqueous ammonium chloride for 20 min to give isopropylidene 1-aminoalkyldenemalonates (**461**) in 53–93% yields (87S480).

The reaction of 2-aminothiazole and isopropylidene bis(methylthio)methylenemalonate (**459**, $R^2 = R^3 = \text{SMe}$) or 1-methylthioalkyldenemalonates (**459**, $R^2 = \text{Me, Et, Ph}$; $R^3 = \text{SMe}$) in boiling ethanol for 2.5 hr or in dimethylformamide at 120–130°C for 4–5 hr, gave 2-substituted 5-oxo-5*H*-thiazolo[3,2-*a*]pyrimidine-6-carboxylates (**462**) in good yields (89S-317). Similarly, in boiling ethanol, 2-substituted 4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxylic acids (**463**) were obtained in 80–85% yields. When anilines were reacted with isopropylidene bis(methylthio)methylenemalonate (**459**, $R^2 = R^3 = \text{MeS}$), (methylthio)(arylamino)methylenemalonates (**464**) were obtained 61–88% yields.

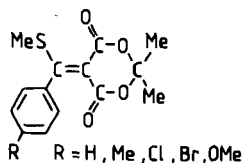


$R = \text{Me, Et, Ph}$

(**462**)



(**463**)



$R = \text{H, Me, Cl, Br, OMe}$

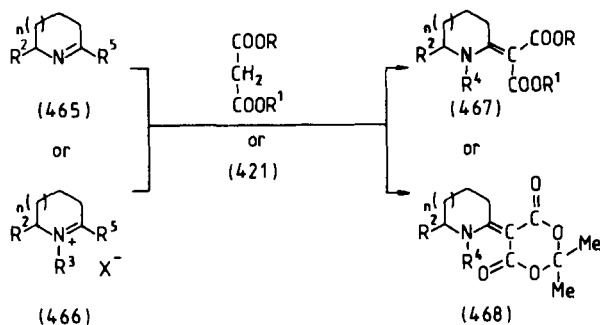
(**464**)

C. Syntheses of 2-Azacycloalkyldenemalonates

1. FROM 2-SUBSTITUTED 1-AZACYCLOALKENES AND MALONATES

1-Phenylpyrrolidinone was first reacted with triethyloxonium fluoborate in methylene chloride at 45°C for 1 hr and then with dimethyl malonate in chloroform at ambient temperature for 48 hr to give dimethyl (1-phenylpyrrolidin-2-ylidene)malonate (**467**, $n = 0$, $R = R^1 = \text{Me}$, $R^2 = \text{H}$, $R^4 = \text{Ph}$) in 4% yield (69JA6683) (Scheme 38).

2-Methylthiopyrrolinium iodides (**466**, $n = 0$; $R^2 = \text{H}$; $R^3 = \text{H, Me}$; $R^5 = \text{SMe}$, $X = \text{I}$) were reacted with diethyl malonate in the presence of potassium iodide and triethylbenzylammonium chloride catalyst in methylene chloride to give diethyl 2-pyrrolidinyldenemalonates (**467**, $n = 0$,



SCHEME 38

$R = R^1 = \text{Et}$, $R^2 = \text{H}$, $R^4 = \text{H, Me}$) in 10% and 55% yields. Under similar conditions, *N*-methylpyrrolidine-2-thione and pyrrolidine-2-thione failed to react [84IJC(B)1176, 84SC533].

Cyclic lactim ethers (465, $n = 0-2$, $R^2 = \text{H}$, $R^5 = \text{OEt}$) were reacted with diethyl malonate in the presence of the acetylacetone nickel complex $[\text{Ni}(\text{acac})_2]$ at 100°C to give diethyl 2-azacycloalkyldenemalonates (467, $n = 0-2$, $R = R^1 = \text{Et}$, $R^2 = R^4 = \text{H}$) in 17–25% yields (86JHC1183).

Dialkyl 2-azepinyldenemalonates (467, $n = 2$, R and $R^1 = \text{Et, } t\text{-Bu}$, $R^2 = R^4 = \text{H}$) were prepared in the reactions of caprolactim methyl ether and dialkyl malonates at 140°C for 3 hr (57MI1).

Lhommet *et al.* studied the reactions of *S*-methylcaprolactim thioether (465, $n = 1$, $R^2 = \text{H}$, $R^5 = \text{SMe}$) and its hydroiodide with malonates ($R = R^1 = \text{Me}$; $R = \text{Et}$, $R^1 = \text{PhCH}_2$ and $t\text{-Bu}$), Meldrum's acid (421), and diethyl monothiomalonate (Scheme 38) (82JHC431). Diethyl monothiomalonate was reacted with 465 and 466 ($n = 2$, $R^2 = \text{H}$; $R^3 = \text{Me}$ and $R^5 = \text{SMe}$; $X = \text{I}^-$) in the presence of triethylamine in boiling benzene for 1 hr (method A) and with the methiodide (466, $n = 2$, $R^2 = \text{H}$, $R^3 = \text{Me}$, $R^5 = \text{SMe}$, $X = \text{I}$) in the presence of triethylamine in boiling chloroform for 1 hr (method B) to afford the diethyl 2-perhydroazepinyldenethiomalonate in 51% and 30% yields, respectively. Dimethyl malonate reacted only under the conditions of method A, while benzyl ethyl malonate reacted only under the conditions of method B to give the corresponding 2-perhydroazepinyldenemalonate (467, $n = 2$, $R = R^1 = \text{Me}$, or $R = \text{Et}$, $R^1 = \text{CH}_2\text{Ph}$, $R^2 = R^4 = \text{H}$) in 22% and 39% yields, respectively. Ethyl, *tert*-butyl malonate ($R = \text{Et}$, $R^1 = t\text{-Bu}$) did not react at all, while Meldrum's acid (421) reacted under both conditions.

Cyclic lactim ethers (465, $n = 0$ and 1, $R^2 = \text{see below}$, $R^5 = \text{OMe}$) were condensed with Meldrum's acid (421) in the presence of a catalytic

amount of $\text{Ni}(\text{acac})_2$ catalyst in chloroform to give isopropylidene 2-azacycloalkylidenemalonates (**468**, $n = 0$ and 1 , $\text{R}^2 = \text{Me}$; $n = 0$, $\text{R}^2 = (\text{CH}_2)_8\text{Me}$ and $(\text{CH}_2)_m\text{CH} = \text{CH}_2$, $m = 4, 7$; $n = 1$, $\text{R}^2 = (\text{CH}_2)_{10}\text{Me}$; $\text{R}^4 = \text{H}$) in 80-87% yields (88FRP2607497, 88TL3061).

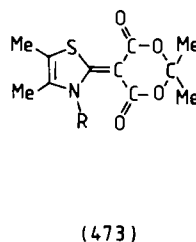
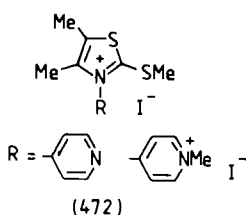
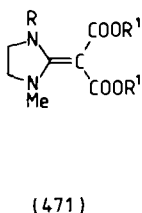
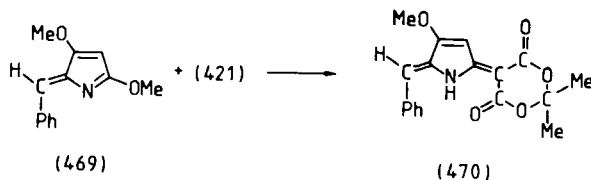
The five- and six-membered isopropylidene 2-azacycloalkylidenemalonates (**468**, $n = 0$ and 1 , $\text{R}^2 = \text{R}^4 = \text{H}$) were prepared in 94% and 76% yields, respectively, in the reactions of Meldrum's acid (**421**) and the appropriate cyclic lactim ether (**465**, $n = 0$ and 1 , $\text{R}^2 = \text{H}$, $\text{R}^5 = \text{OMe}$) in the presence of triethylamine in boiling benzene overnight (79JOC3089). Under these conditions, caprolactim methyl ether did not react, but if the latter reaction was carried out in the presence of acetic acid and piperidine in boiling benzene overnight, a seven-membered cyclic compound (**468**, $n = 2$, $\text{R}^2 = \text{R}^4 = \text{H}$) was obtained in 58% yield (79JOC3089).

Célérier *et al.* investigated the reactions of the hydroiodides of cyclic lactim ethers (**465**, $n = 0-2, 8$; $\text{R}^2 = \text{H}$, $\text{R}^5 = \text{O-alkyl, S-alkyl, Cl}$) and *N*-methyl quaternary salts (**466**, $n = 0-2, 8$; $\text{R}^2 = \text{H}$, $\text{R}^5 = \text{O-alkyl, S-alkyl, Cl}$; $\text{R}^3 = \text{Me, Et, CH}_2\text{Ph, CH}_2\text{COOEt}$) with Meldrum's acid (**421**) (83S195; 88JOC5680) to prepare isopropylidene 2-azacycloalkylidenemalonates (**468**, $n = 0-2, 8$; $\text{R}^2 = \text{H}$, $\text{R}^4 = \text{H, Me, Et, CH}_2\text{Ph, CH}_2\text{COOEt}$) (83S195; 88JOC5680). 2-Alkoxy and 2-alkylthio derivatives (**465** and **466**, $\text{R}^5 = \text{OEt, SMe}$) were reacted in the presence of triethylamine in boiling benzene overnight (83S195), while the 2-chloro derivatives (**466**, $\text{R}^5 = \text{Cl}$) were prepared from cyclic lactams on the action of phosgene in toluene at 0°C for 5 hr, after which Meldrum's acid (**421**) was added, followed by the slow addition of a solution of triethylamine in chloroform. The reaction mixture was stirred at ambient temperature overnight (83S195; 88JOC5680). 2-Chloro derivatives (**465** and **466**, $\text{R}^5 = \text{Cl}$) proved to be the most reactive agents.

1-(3-Chloropropyl)-2-piperidone and 1-(2-chloroethyl)-2-pyrrolidone were reacted with phosgene in toluene, and the 2-chloro derivatives (**466**, $n = 0, 1$, $\text{R}^2 = \text{H}$, $\text{R}^3 = (\text{CH}_2)_m\text{Cl}$, $m = 2, 3$, $\text{R}^5 = \text{Cl}$) were then reacted with Meldrum's acid (**421**) in the presence of triethylamine to give isopropylidene [1-(3-chloroalkyl)piperidin-2-ylidene]malonate and [1-(2-chloroethyl)pyrrolidin-2-ylidene]malonate (**468**, $n = 0, 1$; $\text{R}^2 = \text{H}$; $\text{R}^4 = (\text{CH}_2)_m\text{Cl}$; $m = 2, 3$) in 50% and 60% yields, respectively (87H2335, 89T6161).

2*H*-Pyrrole (**469**) was reacted with Meldrum's acid (**421**) in boiling toluene for 3 hr to afford isopropylidene (3-pyrrolin-2-ylidene)malonate (**470**) in 10% yield (83JHC935).

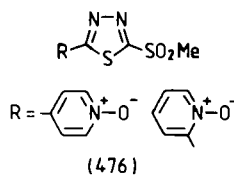
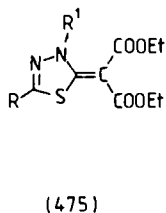
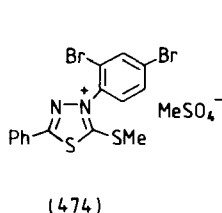
A mixture of 1-methyl-2-methylthio-4,5-dihydro-1*H*-imidazole and diethyl malonate was heated for 54 hr to give diethyl (1-methyl-2-imidazolidinylidene)malonate (**471**, $\text{R} = \text{H}$, $\text{R}^1 = \text{Et}$) in 56% yield (86CB2208).



Dimethyl (1,3-dimethyl-2-imidazolyldiene)malonate (**471**, $R = R^1 = \text{Me}$) was prepared in 24% yield in the reaction of 1,3-dimethyl-2-methylthioimidazolidinium iodide and dimethyl sodiomalonate in dioxane (70ACS3102).

Isopropylidene (1,3-thiazol-2-ylidene)malonates (**473**) were prepared in 52–60% yields in the reactions of (2-methylthio)thiazolium salts (**472**) and Meldrum's acid (**421**) at ambient temperature for 5–10 hr (77KGS341).

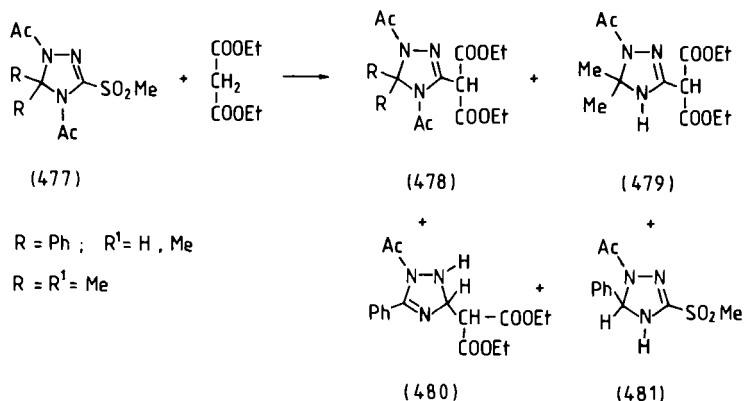
Diethyl malonate was reacted with 2-methylthio-1,3,4-thiadiazolium methosulfate (**474**) in the presence of triethylamine in boiling acetonitrile under nitrogen for 30 min to give diethyl (1,3,4-thiadiazol-2-ylidene)malonate (**475**, $R = \text{Ph}$, $R^1 = 2,4\text{-Br}_2\text{Ph}$) in 48% yield (87CJC2713).



The reactions of 2-methylsulfonyl-1,3,4-thiadiazoles (**476**) and diethyl malonate in the presence of sodium hydride in THF at ambient temperature

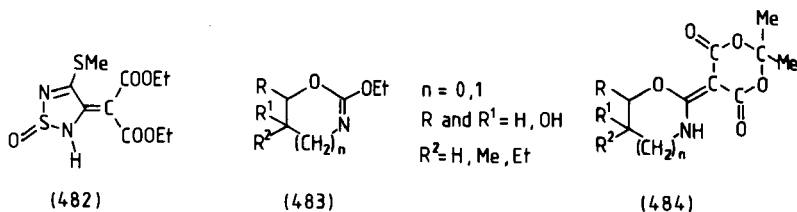
for 3 hr afforded diethyl (1,3,4-thiadiazol-2-ylidene)malonates (**475**, R as in **476**; R¹ = H) in 74% and 83% yields (87CPB1030).

The reactions of 1,4-diacetyl-3-methylsulphonyl-4,5-dihydro-1*H*-1,2,4-triazoles (**477**) with diethyl malonate in THF in the presence of sodium hydride at room temperature or at reflux temperature for 30–60 min led to the formation of diethyl (1,2,4-triazol-3-yl)malonates (**478**) in 42–69% yields (88CPB96). 1,2,4-Triazole derivatives (**479–481**) were also isolated from the reaction mixtures by use of column chromatography in 13–16% yields.



3,4-Di(methylthio)-1,2,5-thiadiazole 1-oxide reacted readily with the carbanion of diethyl malonate to yield (1,2,5-thiadiazol-3-ylidene)malonate (**482**) in high yield [81H(16)1561].

Diethyl (5-nitro-2-pyridyl)malonate was prepared in the reaction of 5-



nitro-2-chloropyridine and diethyl malonate at ambient temperature in DMF in the presence of sodium hydroxide. Dimethyl sulfoxide, *N*-methylpyrrolidone, THF, and dioxane were also used as solvent (88GEP3707361, 88GEP3708093).

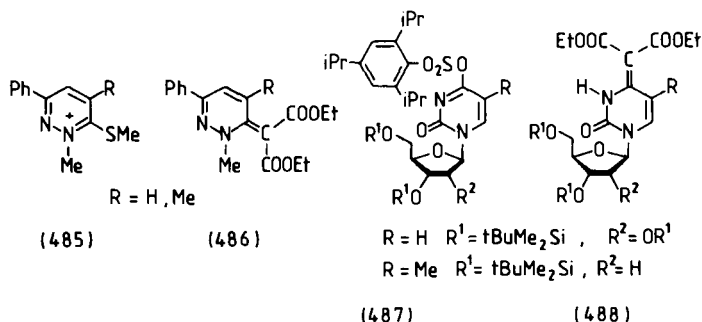
Similarly, 4-pyrimidinylmalonates were obtained in 50–90% yields in the reactions of 4-chloropyrimidines and dialkyl malonates in the presence of sodium hydride in DMF or hexamethylphosphoric triamide at 60–85°C for 2–3 hr (77KGS395; 88ZOR1793, 88ZOR1806).

A diethyl 2-pyrimidinylidenemalonate derivative was prepared in the reaction of the appropriate 2-pyrimidinethione and diethyl malonate (82M12).

1-Ethyl-2-(3-pyridyloxy)pyridinium tetrafluoroborate, prepared from 1-ethyl-2-fluoropyridinium tetrafluoroborate with 3-hydroxypyridine, was reacted with diethyl malonate to give diethyl (1-ethyl-1,2-dihydropyridin-2-ylidene)malonate (85M12).

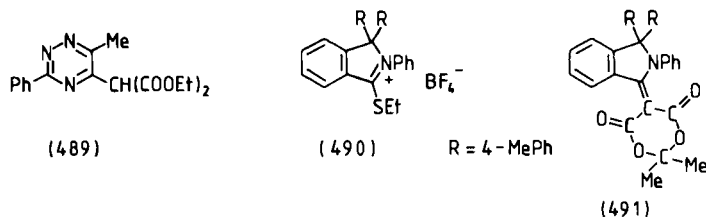
O-Ethyl cyclic carbamates (483) were reacted with Meldrum's acid (421) in boiling chloroform for 24 hr to give isopropylidene (1-oxo-3-azacycloalk-2-ylidene)malonates (484) in 23–39% yields (86JHC701).

The reactions of 3-methylthio-2-methylpyridazinium iodides (485) and diethyl malonate in the presence of potassium carbonate in DMF at room temperature gave diethyl 3-pyridazinyliidenemalonates (486) in 28–46% yields (79TL4837).



The reactions of the sodium salt of diethyl malonate and 4-(triisopropylphenylsulfonyloxy) derivatives of tris-(*tert*-butyldimethylsilyl)uridine (487, $\text{R} = \text{H}$) and di-(*tert*-butyldimethylsilyl)thymidine (487, $\text{R} = \text{Me}$) in THF at 0°C afforded the corresponding diethyl 4-pyrimidinylidenemalonates (488) in 88–89% yields (87TL2821).

The reaction of 5-chloro-6-methyl-3-phenyl-1,2,4-triazine and diethyl malonate in the presence of sodium hydride in THF at ambient temperature for 12–24 hr gave malonate (**489**) in 65% yield (87H3259).



1-Ethylthioisoinidolium salt (**490**) was reacted with Meldrum's acid in the presence of triethylamine in methylene chloride for 24 hr to give isopropylidene 1-isoinidolylidenemalonate (**491**) in 51% yield (87K-GS199).

Dimethyl malonate was added to a suspension of sodium hydride in THF at room temperature, and after 10 min, 2-methylthio-1-methylquinolinium iodide was added. The reaction mixture was stirred for 1.5 hr at ambient temperature to give dimethyl (1-methyl-1,2-dihydro-2-quinolinylidene)malonate in 95% yield [81H(15)277].

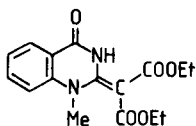
2-Chloro- and 2-methylthio-1-methylquinolinium iodides were reacted with dimethyl malonate in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in DMF at 80°C for 1 hr, or in the presence of triethylamine for 5 hr, to afford dimethyl (1-methyl-1,2-dihydro-2-quinolinylidene)malonate (86M13). The use of DBU and the 2-methylthio derivative gave a better yield than that from triethylamine and the 2-chloro derivative.

Dimethyl and diethyl (1-methylpyrrolidin-2-ylidene)malonates (e.g., Scheme 38, **467**, $n = 0$, $R = R^1 = \text{Me, Et}$; $R^2 = \text{H}$; $R^4 = \text{Me}$) and diethyl (1-methyl-1,2-dihydroquinolin-2-ylidene)malonate were obtained in 30–52% yields when 1-methylpyrrolidin-2-one and 1-methyl-1,2-dihydroquinolin-2-one were first reacted with phosgene and then with dialkyl malonates in the presence of triethylamine in benzene at 60°C (61CB2278; 69JA6683).

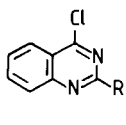
The reaction of 2-chloroquinoxaline and diethyl malonate in the presence of sodium amide or potassium hydroxide in hexamethylphosphoramide at room temperature for 0.5 hr, or at 50°C for 1.5 hr, gave diethyl 2-quinoxalylmalonate in 52% and 53% yields, respectively (88YZ586). No reaction occurred if the reaction was carried out in the presence of sodium amide in benzene.

2-Cyano-1-methyl-1,4-dihydroquinazolin-4-one was allowed to react

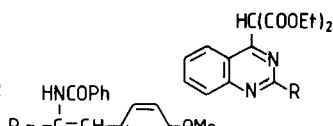
with the sodium salt of diethyl malonate in THF at room temperature for 1 hr to give diethyl 2-quinazolinylidenemalonate (**492**) in 71% yield (83CPB2234).



(492)



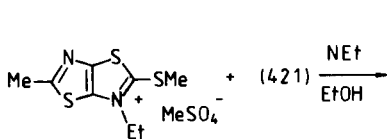
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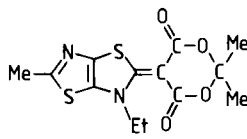
(494)

2-Substituted 4-chloroquinazoline (**493**) was reacted with diethyl malonate in boiling DMF for 5 hr in the presence of sodium amide to give 4-quinazolinylmalonate (**494**) in 65% yield [88IJC(B)920].

Meldrum's acid (**421**) was reacted with 2-methylthiothiazolo[5,4-*d*]-thiazolium salt (**495**) in the presence of triethylamine in ethanol at room temperature for 48 hr to give (thiazolothiazolinyldene)malonate (**496**) in 55% yield (74UKZ1331).

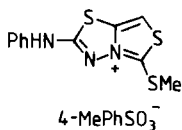


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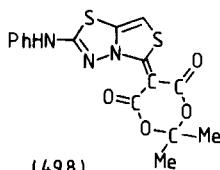


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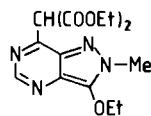
The reaction of isopropylidene malonate (**421**) and 2-phenylamino-5-methylthiothiazolo[4,3-*b*]-[1,3,4]thiadiazolinium tosylate (**497**) in the presence of triethylamine in DMF at 55°C for 3 hr afforded a merocyanine derivative (**498**) in 92% yield (81UKZ295).



(497)



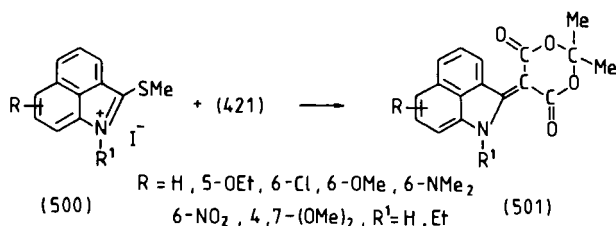
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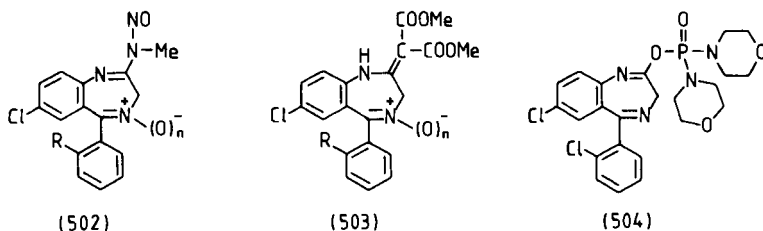
(499)

7-Chloro-3-ethoxy-2-methyl-2*H*-pyrazolo[4,3-*d*]pyrimidine was reacted with the sodium salt of dimethyl malonate in DMF to give (pyrazolo[4,3-*d*]pyrimidin-7-yl)malonate (**499**) [88JAP(K)246377].

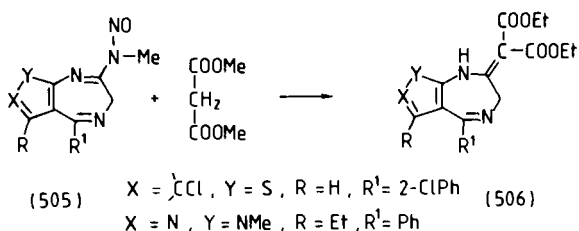
2-Methylthiobenz[*cd*]indolium iodides (**500**) were reacted with Meldrum's acid (**421**) in the presence of sodium acetate or triethylamine in ethanol at 50°C for 1.5 hr to give isopropylidene (benz[*cd*]indol-2-ylidene)malonates (**501**) in 76–94% yields (81MI2; 82ZOR435).



Dimethyl malonate was reacted with 2-(*N*-nitrosomethylamino)-1,4-benzodiazepines (**502**, $\text{R} = \text{H}, \text{F}; n = 0, 1$) in the presence of potassium *tert*-butoxide in DMF under nitrogen to give (1,4-benzo(*b*)diazepin-2-ylidene)malonates (**503**, $\text{R} = \text{H}, \text{F}; n = 0, 1$) (75JOC153; 83USP4401597). A dichloro derivative of (1,4-benzodiazepin-2-ylidene)malonate (**503**, $\text{R} = \text{Cl}, n = 0$) was prepared in the reaction of a 1,4-benzodiazepine derivative (**504**) and dimethyl malonate under the previous conditions (83USP4401597).

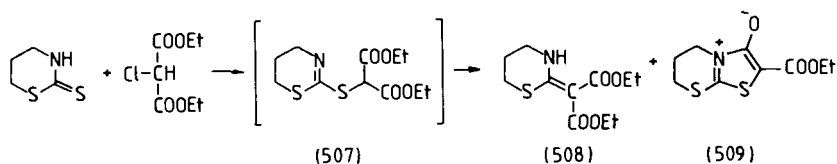


Thieno[2,3-*e*]-1,4-diazepine (**505**, $\text{X} = \text{CCl}; \text{Y} = \text{S}; \text{R} = \text{H}; \text{R}^1 = 2\text{-ClPh}$) and pyrazolo[3,4-*e*]-1,4-diazepine (**505**, $\text{X} = \text{N}, \text{Y} = \text{NMe}, \text{R} = \text{Et}, \text{R}^1 = \text{Ph}$) were reacted with dimethyl malonate in the presence of potassium *tert*-butoxide in DMF under nitrogen to give the corresponding (condensed 1,4-diazepin-2-ylidene)malonates (**506**) (83USP4401597).

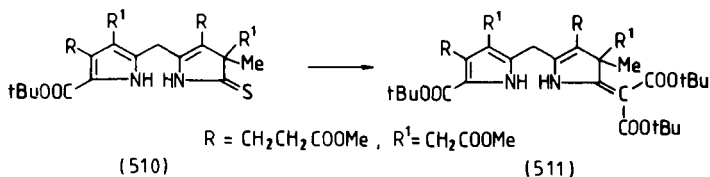


2. FROM DIALKYL 2-HALOMALONATES

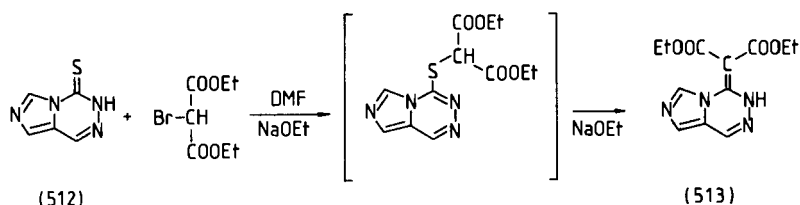
The reaction of tetrahydro-1,3-thiazine-2-thione and diethyl 2-chloromalonate in the presence of triethylamine in boiling methylene chloride for 1.5 hr gave tetrahydro-1,3-thiazin-2-ylidenemalonate (**508**) in 33% yield via **507** through Eschenmoser sulfur elimination, together with traces of the mesoionic derivative (**509**) [77JCS(P1)1107]. In a similar reaction, diethyl 2-bromomalonate afforded the mesoionic compound (**509**) in 80% yield. Tetrahydro-1,3-thiazin-2-ylidenemalonate (**508**) was also obtained in 42% yield from **509** by irradiation in the presence of tributylphosphine in ethanol for 15 hr under argon [77JCS(P1)1107].



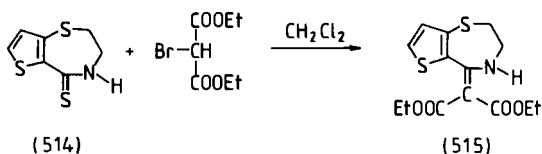
The tri-(*tert*-butyl) ester (**511**) was prepared in 40% yield when the thiolactam (**510**) was first treated with di-*tert*-butyl malonate and DBU and then with triphenylphosphine and DBU in boiling toluene (85CC583).



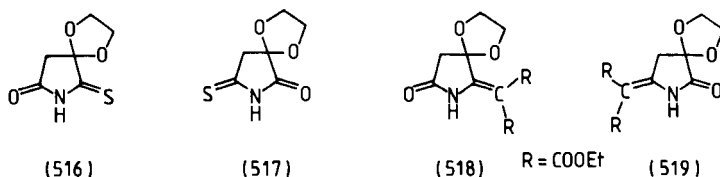
The reaction of the sodium salt of imidazo[1,5-*d*][1,2,4]triazinethione (**512**) and diethyl 2-bromomalonate in dimethylformamide at room temperature overnight gave (imidazotriazinylidene)malonate (**513**) in 14% yield (85JMC1704).



3,4-Dihydrothieno[2,3-*f*]-1,4-thiazepin-5(2*H*)-thione (**514**) was reacted with diethyl 2-bromomalonate in methylene chloride under argon for 2.5 hr. The reaction mixture was then treated with a 10% aqueous solution of potassium hydrogen carbonate for 30 min to give (thienothiazepinylidene)malonate (**515**) (86EUP183994).

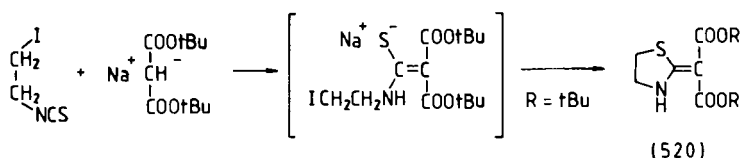


The reaction of diethyl bromomalonate with a 3 : 1 mixture of pyrrolidinethiones (**516** and **517**) in the presence of sodium ethoxide gave a 3 : 1 mixture of isomeric (2- and 5-pyrrolidinylidene)malonates (**518** and **519**) in 73% yield (89H435).

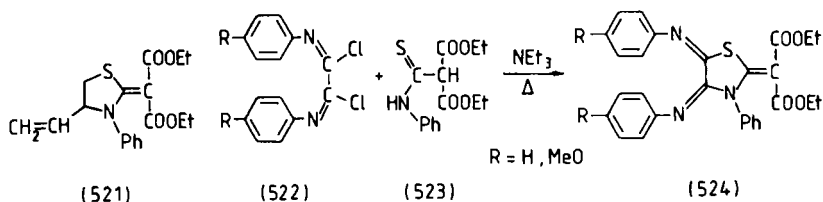


3. FROM 2-(AMINOTHIOCARBONYL)MALONATES AND [2-(ALKYLTHIO)THIOCARBONYL]MALONATES

Di-(*tert*-butyl) sodiomalonate was reacted with 2-iodoethyl isothiocyanate in diethyl ether at ambient temperature for 10–18 hr to give 2-thiazolidinylidenemalonate (**520**, R = *t*Bu) in 69% yield after chromatography (85AJC745).



Diethyl malonate was first treated with sodium hydride in DMF at 0°C, then with phenyl isothiocyanate at 25°C, and subsequently with *Z*-1,4-dichlorobut-2-ene to give (3-phenyl-4-vinylthiazolidin-2-ylidene)malonate (**521**) in 36% yield (85EGP227705).

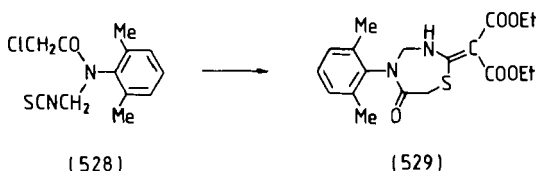
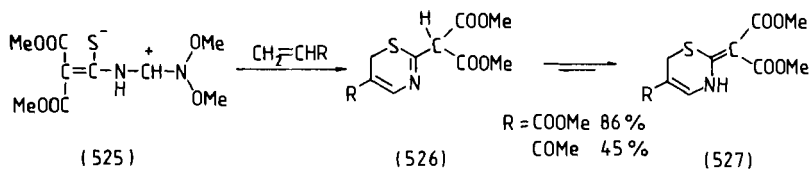


Thiocarboxamide (**523**) was reacted with *N,N'*-diaryloxalylimidoyl chlorides (**522**) in the presence of triethylamine in boiling acetonitrile or acetone for 1 hr to give diethyl [4,5-di(arylimino)thiazolidin-2-ylidene]malonates (**524**) in 44–68% yields (87EGP249014).

Diethyl malonate was reacted with 4-chlorophenyl isothiocyanate in the presence of sodium hydride in dioxane at room temperature for 1 hr to give the sodium salt of mercapto-(4-chlorophenylamino)methylenemalonate, which was then treated with ethylene dibromide in DMF at room temperature overnight. In this way, diethyl [3-(4-chlorophenyl)-1,3-thiazolidin-2-ylidene]malonate was obtained in 88% yield (82EUP58392).

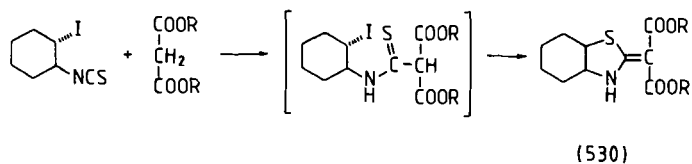
The reaction of dimethyl (aminothiocarbonyl)malonate with DMF dimethyl acetal in benzene at ambient temperature for 2 hr gave a zwitterion (**525**) in 95% yield. [4 + 2] Cycloaddition of this zwitterion (**525**) and

acrylic dienophiles afforded (1,3-thiazin-2-yl)malonates (**526**), which exhibited equilibrium with (1,3-thiazin-2-ylidene)malonates (**527**) [83PS-(15)143].

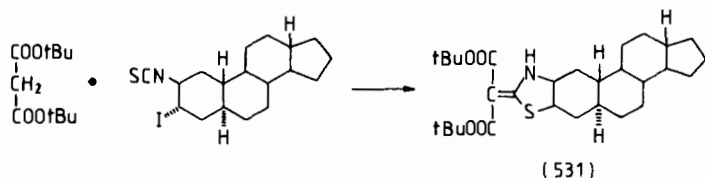


Diethyl sodiomalonate, prepared from diethyl malonate and sodium hydride, was reacted with isothiocyanate (**528**) in DMF by dropwise addition at 5°C. The reaction mixture was then stirred at ambient temperature for 1 hr to give (1,3,5-thiadiazepin-2-ylidene)malonate (**529**) in 76% yield (86S817).

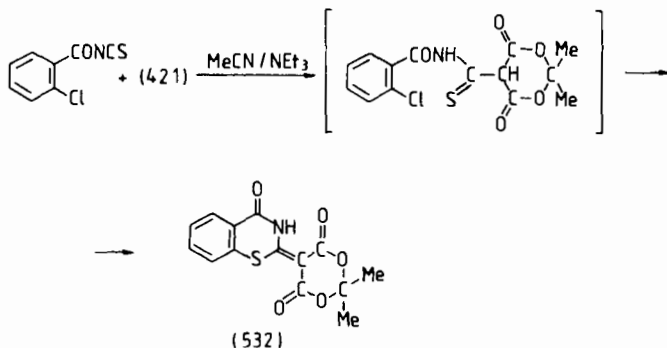
In the reactions of *trans*-2-iodocyclohexyl isothiocyanate and dialkyl malonates in the presence of sodium hydride in diethyl ether, or in the presence of butyllithium in THF at room temperature for 10–20 hr, 2-(*cis*-octahydrobenzothiazol-2-ylidene)malonates (**530**) were obtained in 69–87% yields (85AJC745).



A similar reaction was carried out with 3 α -iodo-5 α -androstan-2 β -yl isothiocyanate and di-(*tert*-butyl) malonate to give (andost-2-eno[2,3-*d*]thiazol-2-ylidene)malonate (**531**) in 84% yield (85AJC745).



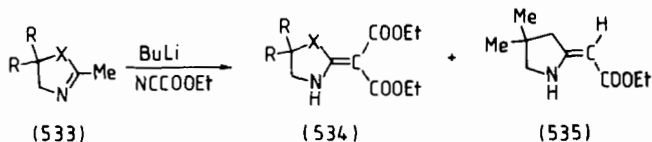
Meldrum's acid (**421**) was reacted with 2-chlorobenzoyl isocyanate in the presence of triethylamine in boiling acetonitrile for 40 min to give isopropylidene (1,3-benzothiazin-2-ylidene)malonate (**532**) in 26% yield (87ZC68).

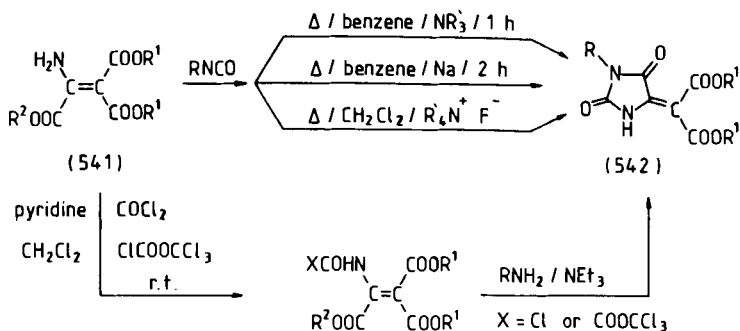


Dimethyl 2-[(methylthio)thiocarbonyl]malonate was reacted with ethylenimine in boiling ethanol for 24 hr to give dimethyl (thiazolidin-2-ylidene)malonate (**520**, R = Me) in 51% yield (69T4649).

4. MISCELLANEOUS

The reaction of 2-methyl-1-pyrroline (**533**, R = R = Me, X = CH₃) and 2-methyl-2-imidazoline (**533**, R = H, X = NPh), first with butyllithium in THF at -70°C and then with ethyl cyanoformate, afforded diethyl 2-pyrrolidinylidene- and 2-imidazolidinylidenemalonates (**534**; R = Me,

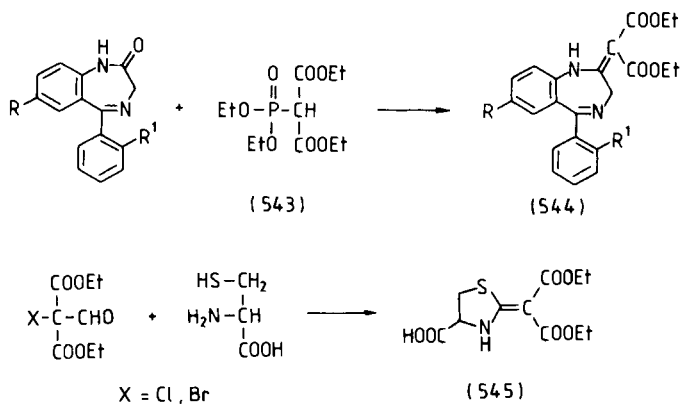




SCHEME 39

(2,5-Dioxoimidazolidin-4-ylidene)malonates (**542**) were prepared in good yields in the reactions of amino(alkoxycarbonyl)methylenemalonates (**541**) and isocyanates in the presence of a tertiary amine in boiling benzene for 1 hr [82JAP(K)58673], or in the presence of sodium for 2 hr [82JAP(K)64679], or in the presence of a quaternary ammonium fluoride and triethylamine in methylene chloride at ambient temperature for 20 hr [82EUP49841, 82EUP52341], or at reflux temperature for 6 hr [82JAP(K)59873]. Compounds **542** were also prepared in the reactions of **541** with phosgene in the presence of pyridine in methylene chloride [82EUP49841, 82EUP52341, 82JAP(K)59874] or with trichloromethyl chloroformate [82JAP(K)59874] at ambient temperature, then with amines in the presence of triethylamine (Scheme 39).

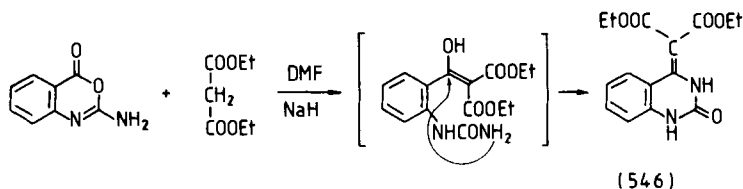
The reaction product (**543**) of diethyl malonate and diethyl chlorophosphate was reacted with 1,4-benzodiazepin-2-ones in the presence of sodium hydride in THF at ambient temperature to give (1,4-benzodiazepin-2-ylidene)malonates (**544**) (81EUP38423).



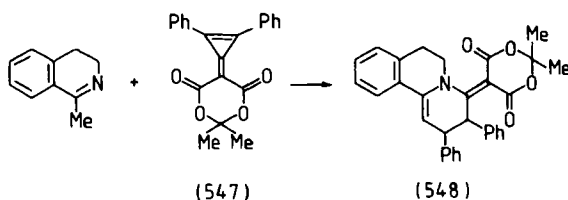
The reactions of L-cysteine and diethyl 2-formyl-2-halomalonates yielded (thiazolidin-2-ylidene)malonate (**545**) (84USP626960).

(2-Oxo-1,2,3,4-tetrahydropyrimidin-4-ylidene)malonate was prepared [86JAP(K)43739].

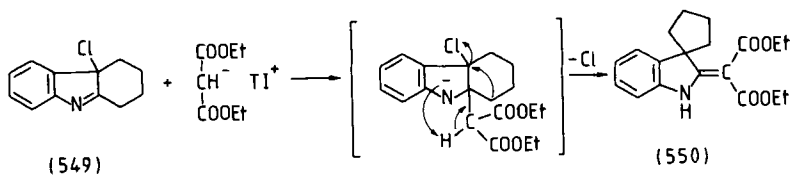
2-Amino-3,1-benzoxazin-4-one was reacted with diethyl malonate in the presence of sodium hydride in dimethylformamide at ambient temperature for 4 hr to give 4-quinazolinylidenemalonate (**546**) in 28% yield [83JCS(P1)813].



The reaction of 1-methyl-3,4-dihydroisoquinoline and triafulvene (**547**) in boiling ethanol for 24 hr gave isopropylidene benzoquinolizinylidene-malonate (**548**) in 65% yield (86S908).



The reaction of 4a-chlorotetrahydrocarbazole (**549**) and thallium(I) malonate in boiling benzene for 18 hr gave spiro-malonate (**550**) in 47% yield (78JOC3702).



Dimethyl 2-pyridylmalonate was prepared in 40% yield in the reaction of methyl 2-pyridylacetate and dimethyl carbonate in diethyl ether in the presence of sodium hydride at room temperature for 4 hr (88ZOR1799).

Cyclization of 1-Aminoalkylidenemalonates

A. Cyclization of Dialkyl Aminoalkylidenemalonates

1. ON THE ACTION OF HEAT

The thermal ring closure of *N*-(het)arylaminomethylenemalonates gave bi- or polycondensed 4-hydroxypyridine-3-carboxylates. This type of reaction is named the Gould–Jacobs reaction. (The reaction is illustrated in Scheme 40). The cyclized products may exhibit oxo-enol tautomerism. In this review, the hydroxy form is generally depicted. This type of tautomerism was discussed in an excellent review (76M11).

Ring closure can be effected on the action of heat in the melt under atmospheric (e.g., 36JCS428; 37JCS867; 46JA1204, 46JA1272) or reduced pressure (49JIC171) or in a high-boiling solvent, sometimes under an inert atmosphere (e.g., nitrogen, 39JA2890; 46JA1268, 46JCS1033) at a temperature of around 250–270°C. The alcohol formed is usually distilled off from the reaction (e.g., 46JA1264). The solvent is sometimes preheated, especially in large-scale experiments (e.g., 46JA1204, 46JA1264, 46JA1268).

As the high-boiling solvent, mineral oil (e.g., 39JA2890; 46JA1264; 49JCS1017; 67USP3320257), Finol (46JA1264), diphenyl ether (e.g., 46JA1204, 46JA1268), liquid paraffin (e.g., 46JCS1033; 48JCS893; 70MIP3; 78JPR937; 79EGP136742), diethyl phthalate (e.g., 62BEP612258; 67USP3320257), tridecane (e.g., 84JHC673), dodecylbenzene (e.g., 68BRP1122715; 69GEP1908262), trichlorobenzene (e.g., 72JMC1203), dichlorobenzene (59JOC779), Gilotherm (e.g., 78GEP2822124), Dowtherm A (e.g., 46JA1264) dibenzylbenzene (Marlotherm, e.g., 74BEP819195; 75GEP2343462), and decaline (69T4649) have been used. Dowtherm A (b.p. 260°C) is used most widely; this is a eutectic mixture of diphenyl ether (73.5%) and biphenyl (26.5%). It is superior to pure diphenyl ether (m.p. 26–27°C) because of its lower freezing point (12°C) (e.g., 46JA1204, 46JA1264). The cyclization can be carried out above 300°C when dibenzylbenzene is used as solvent.

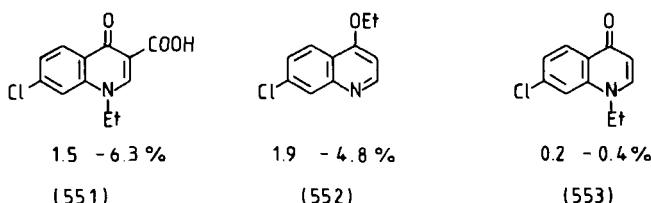
The volume of solvent used in the cyclization may be varied considerably, depending on the solubility of the aminomethylenemalonate. The purity of the cyclization product is generally higher when the cyclization is carried out at a higher temperature for a shorter reaction period, as



SCHEME 40

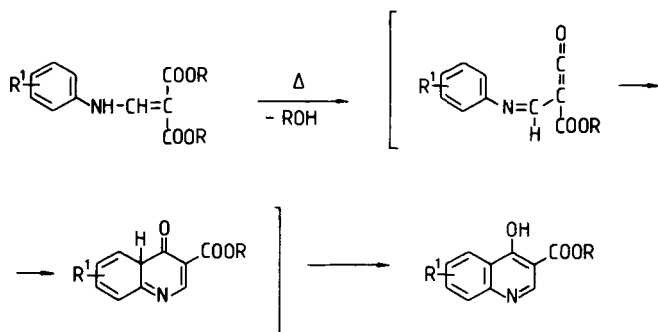
opposed to when the cyclization is conducted at a lower temperature for a longer time.

Raychaudhuri and Basu investigated the formation of side products in the large-scale cyclization of diethyl *N*-(3-chlorophenyl)aminomethylenemalonate (**250**) in diphenyl ether (70JIC25). As side products, 7-chloro-1-ethyl-1,4-dihydro-4-oxoquinoline-3-carboxylic acid (**551**), 7-chloro-4-ethoxyquinoline (**552**), and 7-chloro-1-ethyl-4(1*H*)-quinoline (**553**) could be isolated. These were probably formed from the primarily cyclized product, ethyl 7-chloro-4-hydroxyquinoline-3-carboxylate. The quantities of the side products depended on the reaction temperature during the cyclization, the duration of heating, and the purity of the starting *N*-(3-chlorophenyl)aminomethylenemalonate (**250**).



The cyclized product usually precipitates from the reaction mixture in crystalline form at room temperature. The precipitation of the product may be completed by adding light petroleum, ligroin, or hexane to the reaction mixture (e.g., 51JOC1414; 56BRP743901, 56JCS3079).

In the thermal cyclization of *N*-(het)arylamino methylenemalonates, the iminoketene may be regarded as the first intermediate (Scheme 41), because the cyclization occurs in a relatively narrow temperature range (generally 230–270°C) (at higher temperature, decomposition becomes significant), and aminomethylenemalonates containing a disubstituted amino group can practically not be cyclized thermally. Furthermore, the product ratio obtained for *N*-(3-substituted phenyl)aminomethylenemalonates differs considerably from those obtained under acidic cyclization conditions (see Section A.2, this chapter).

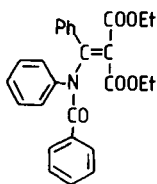


SCHEME 41

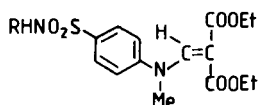
N,N-(Disubstituted amino)methylenemalonates (e.g., **554–558**) were reported to fail to cyclize to the corresponding condensed pyridinecarboxylates [e.g., 36JCS428; 71JHC357; 73CI(M)542; 75JCS(P1)2409; 76FES237; 88JHC231].

Diethyl *N,N*-diphenylaminomethylenemalonate (**112**, $R = R^1 = H$) was heated in diphenyl ether at reflux temperature for 1 hr to give ethyl 1-phenyl-4-oxo-1,4-dihydroquinoline-3-carboxylate (**559**) in only 9% yield (69BRP1147336). For other *N,N*-diarylaminoalkylidenemalonates, this procedure was completely unsuccessful.

However, it was claimed that the thermal cyclization of (7,8-difluoro-3-fluoromethyl-2,3-dihydro-1,4-benzoxazin-4-yl)methylenemalonate (**560**) in diphenyl ether at 250°C for 30 min gave pyrido[1,2-*de*]-1,4-benzoxazine-6-carboxylate (**561**) in 71% yield [86JAP(K)204188].

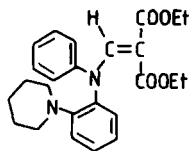


(554)

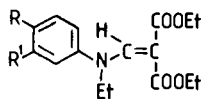


$R = H, Me, 2\text{-pyridyl}$

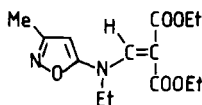
(555)



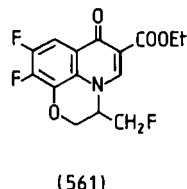
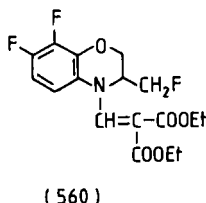
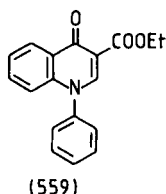
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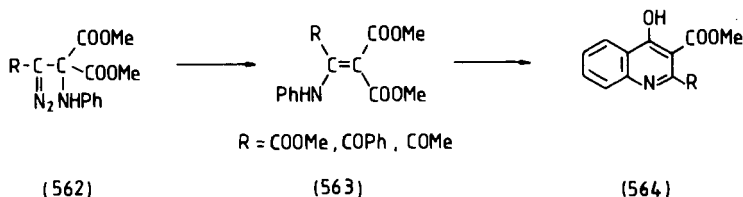
The cyclization of 1-(arylamino)alkylidenemalonates (Scheme 40, $R^2 \neq H$) generally proceeds more smoothly than that of *N*-arylaminomethylenemalonates (Scheme 40, $R^2 = H$). For example, diethyl phenyl(arylamino)methylenemalonates (**6**) were cyclized by heating in the melt above 150°C to afford 2-phenylquinolinecarboxylates (**7**) (36JCS428), while (arylamino)aminomethylenemalonates (Scheme 40, $R^2 = H$) could be cyclized by heating above 200°C (e.g., 46JA1204).

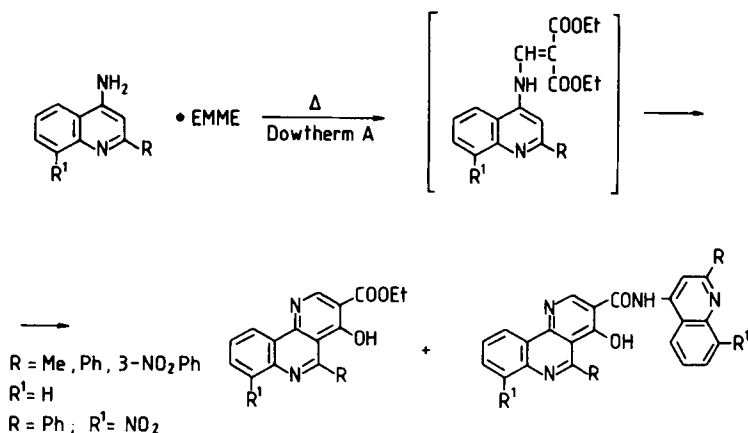
Later, different ethyl 4-hydroxy-2-arylquinoline-3-carboxylates were prepared by this route, by heating aryl(phenylamino)methylenemalonates in the melt at 150 – 160°C under reduced pressure (49JIC171).

Methyl 2-substituted 4-hydroxyquinoline-3-carboxylates (**564**) were prepared in 41–54% yields by heating diazo derivatives (**562**) in boiling toluene for 0.5–9 hr, via aminomethylenemalonates (**563**). ^1H -NMR investigation revealed the formation of a 52 : 48 mixture of aminomethylenemalonate (**563**, $R = \text{COPh}$) and quinolinecarboxylate (**564**, $R = \text{COPh}$) when the diazo compound (**562**, $R = \text{COPh}$) was heated in toluene for 4 hr. A better yield was achieved when the triester (**562**, $R = \text{COOMe}$) was heated in boiling 1,2-dichlorobenzene (80T1821).

When diethyl phenyl(phenylamino)methylenemalonate (**4**) was heated in the presence of *p*-toluidine at 150°C , the *N*-(4-methylphenyl)amide of 2-phenylquinoline-3-carboxylate (**7**, $R = H$) was obtained (36JCS428).

The amine and EMME were sometimes reacted in a high-boiling solvent (e.g., Dowtherm A, diphenyl ether, paraffin oil) at lower temperature, and the condensation product was then cyclized without isolation by raising the temperature of the solvent [e.g., 46JA1232; 49JCS1017; 50JCS464, 50JCS1224; 58JCS828; 59JOC779; 67USP3316147; 72ACH469, 72JMC





SCHEME 42

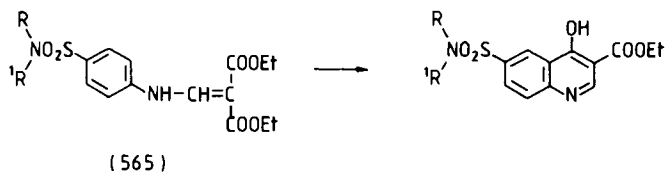
1203; 79MI5, 79USP4137227; 82IJC(B)444]. However, in this case, the cyclized ester might be accompanied by amide (e.g., 46JCS1033; 58JCS 828; also Scheme 42).

4-Substituted anilines were reacted with EMME in diphenyl ether by heating to 185°C, with distillation of the ethanol formed. The temperature of the reaction mixture was then raised to 245°C and the reaction mixture was heated at 245°C for 1 hr to give ethyl 6-substituted quinoline-3-carboxylates in good yields (85USP4560692).

A catalytic amount of salt (e.g., ZnCl_2 , zinc acetate, NiSO_4 , CoCl_2) increased the rate of the cyclization reaction (72ACH4469).

Chapter 7 (Section D) lists some ring systems prepared by the thermal cyclization of dialkyl aminomethylenemalonates.

The unsuccessful thermal cyclization of (4-sulfamidophenyl)aminomethylenemalonate (**565**, $R = R' = \text{H}$) was reported (47JA855), but heating of its (*N*-substituted 4-sulfamido)phenyl derivatives (**565**, $R \neq \text{H}$, $R' = \text{H}$) (58MI1; 73CI(M)542; 76FES237) and *N,N*-disubstituted derivatives (**565**, $R \neq \text{H}$, $R' \neq \text{H}$) (68SAP6075) in Dowtherm A gave the expected quinoline-3-carboxylate in 30–71% yields.



Cyclization did not occur with (sulfamidophenyl)aminomethylenemalonates (**565**) (containing $R=6\text{-chloropyridazin-3-yl}$, $3\text{-methylisoxazol-5-yl}$ or $2\text{-methylthiazol-5-yl}$, $R^1 = H$) at 250°C because of the thermal instability of the aminomethylenemalonates (76FES237). At a lower temperature in Dowtherm A or in diethyl phthalate at $170\text{--}180^\circ\text{C}$, they remained unaltered.

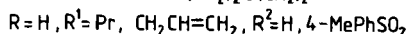
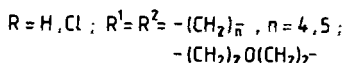
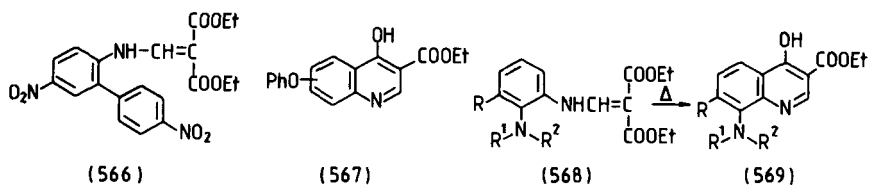
N-[4-Nitro-2-(4-nitrophenyl)phenyl]aminomethylenemalonate (**566**) was not cyclized in Dowtherm A or on the action of sulfuric acid and phosphoric acid (50JCS464). Likewise, diethyl *N*-(4-methoxy-5-methyl-2-nitrophenyl)aminomethylenemalonate could not be cyclized by heating in Dowtherm A (80JPS933).

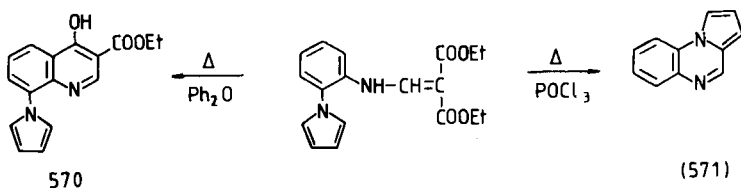
In the cyclization of phenoxy derivatives of (phenylamino)methylenemalonate (**253**, $R = \text{PhO}$), Finol, a light mineral oil, was used as a high-boiling solvent because of the high solubility of the phenoxyquinoline-3-carboxylates (**567**) in Dowtherm A (46JA1264).

The thermal cyclization of *N*-[2-(disubstituted amino)phenyl]aminomethylenemalonates (**568**, $R^1 \neq H$, $R^2 \neq H$) by heating in boiling diphenyl ether for 5–18 min afforded quinolines (**569**, $R^1 \neq H$, $R^2 \neq H$) in 53–81% yields [75JCS(P1)2409]. *N*-[2-(Substituted amino)phenyl]aminomethylenemalonates (**568**, $R^1 \neq H$, $R^2 = H$) failed to cyclize to the corresponding quinolines (**569**, $R^1 \neq H$, $R^2 = H$) when heated in diphenyl ether, but their *N*-(*p*-tosyl) derivatives (**568**, $R^2 = 4\text{-MePhSO}_2$) gave the expected products (**569**, $R^2 = 4\text{-MePhSO}_2$) in 72–77% yields.

The cyclization of diethyl *N*-[2-(1-pyrrolyl)phenyl]aminomethylenemalonate by heating in diphenyl ether for 8 min gave 8-pyrrolylquinoline-3-carboxylate (**570**) in 23% yield, while its reaction in boiling phosphoryl chloride for 15 min afforded the tricyclic pyrroloquinoxaline (**571**) in 76% yield [75JCS(P1)2409].

The thermal cyclization of bis(aminomethylenemalonate) (**572**) in boiling Dowtherm A for 20 min gave bis(quinolinecarboxylate) (**573**) in only 4% yield (46JA1264).

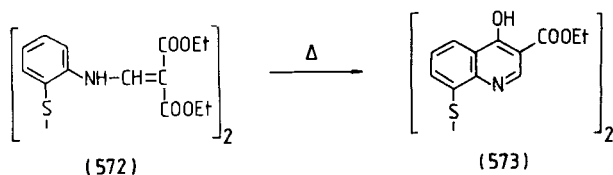




Bis condensation products (**160**) were thermally cyclized to give bis-(quinolines) (**574**, R and Z as in **160**) [84M11, 84M15; 86M110].

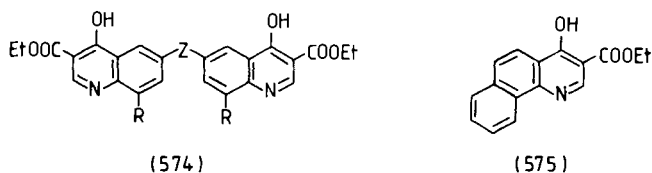
Benzo[*h*]quinoline-3-carboxylate (**575**) was prepared in 88–94% yields by the thermal cyclization of diethyl 1-naphthylaminomethylenemalonate in diphenyl ether or liquid paraffin oil for 50–60 min (46JA1327; 48JCS893).

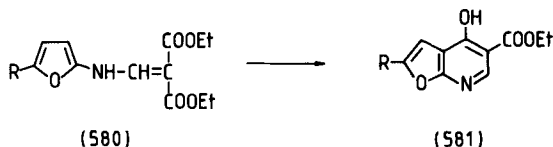
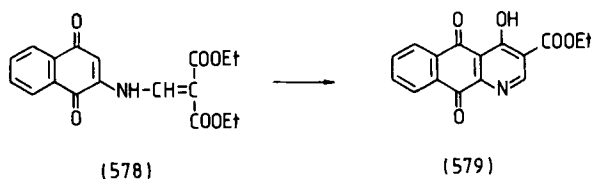
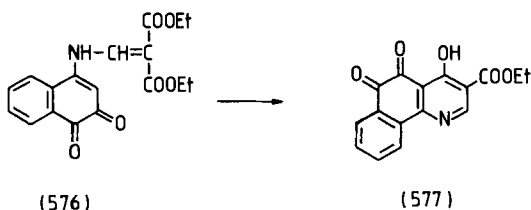
The reaction of (naphthoquinonylamino)methylenemalonates (**576** and **578**) in boiling Dowtherm A for 45 min afforded benzo[*g*]- and benzo[*h*]-quinolinecarboxylates (**577** and **579**) in 50% and 50%, yields, respectively (67JOC3210).



Furo[2,3-*b*]pyridine-5-carboxylates (**581**) were obtained from 2-furylaminomethylenemalonates (**580**) by heating in Dowtherm A (66JHC202).

When heated in diphenyl ether at 190–220°C for 40 min, in boiling Dowtherm A for 10 min, or in polyphosphate at 120–150°C for 30 min, 2-thienylaminomethylenemalonates (**582**, R² = H) and *N*-(4,5-cycloalkylidenethien-2-yl)aminomethylenemalonates [**582**, R = R¹ = (CH₂)_{*n*}, *n* = 3,4; R² = H] underwent thermal cyclization to give thieno[2,3-*b*]pyridines (**583**), cyclopenta[1',2' : 2,3]thieno[5,4-*b*]pyridines [**583**, R = R¹ = —(CH₂)₃—] and tetrahydrobenzothieno[2,3-*b*]pyridine [**583**, R = R¹ = —(CH₂)₄—]. Cyclizations also took place with carboxylic acids (**582**, R² = COOH) as starting materials [75GEP2435025, 75JAP(K)77393,

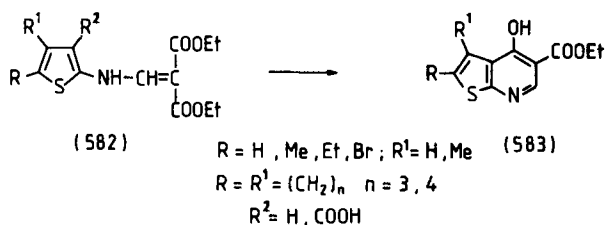




75JAP(K)77394; 76GEP2447477, 76JAP(K)48440, 76JAP(K)101127, 76JAP(K)101128; 78BEP858479, 78MI3].

Thieno[2,3-*b*]pyridine-5-carboxylate (**583**, $R = R^1 = H$) was also obtained in 61% yield on the thermal cyclization of the *tert*-butoxycarbonyl derivative (**582**, $R = R^1 = H$, $R^2 = COOtBu$) in boiling Dowtherm A for 10 min (76GEP2447477).

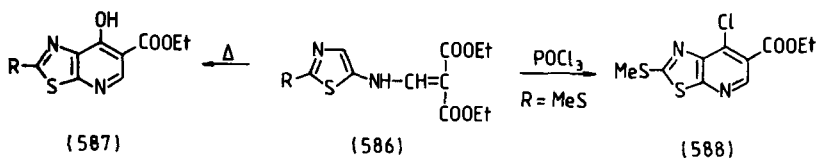
The cyclization of 5-isoxazolylaminomethylenemalonates (**584**, $X = O$, $R = Me, Ph$) in diphenyl ether at reflux temperature for 7–10 min gave isoxazolo[5,4-*b*]pyridines (**585**, $X = O$, $R = Me$) in 48–56% yields (72AP833, 72GEP2213076, 72GEP2213077; 73GEP2237765, 73GEP2301267, 74GEP2329809; 75USP3862947, 75USP3912737, 75USP3925388; 88JHC231).





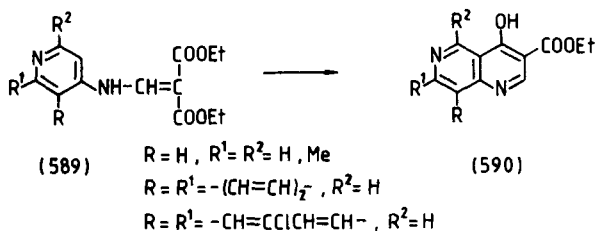
5-Isothiazolylaminomethylenemalonates (**584**, X = S, R = Me, Ph, 4-MeOPh) were cyclized in diphenyl ether at reflux temperature for 10–45 min to afford isothiazolo[5,4-*b*]pyridinecarboxylates (**585**, X = S, R = Me, Ph, 4-MeOPh) in 78–95% yields [80JHC717; 82IJC(B)458].

N-(2-Methylthio-5-thiazolyl)aminomethylenemalonate (**586**, R = MeS) was cyclized by heating in diphenyl ether at 250°C for 10 min to give 4-hydroxythiazolo[5,4-*b*]pyridine (**587**, R = MeS) in 90% yield, and in boiling phosphoryl chloride for 3 hr to afford 4-chlorothiazolo[5,4-*b*]pyridine-5-carboxylate (**588**) in 53% yield (84JHC401).



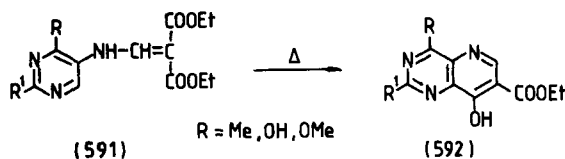
5-Thiazolylaminomethylenemalonates (**586**, R = H, Me, Ph) were cyclized by heating in boiling diphenyl ether for 5 min to yield thiazolo[5,4-*b*]pyridines (**587**, R = H, Me, Ph) (71JAP43792).

The cyclizations of 4-pyridinylamino(50JOC1224; 57MI3; 65USP3225 055) and 4-quinolinylaminomethylenemalonates (**589**) (50JOC1224; 70JMC230) were carried out in boiling Dowtherm A for 4–30 min to give 1,6-naphthyridine derivatives (**590**) in 83–93% yields.

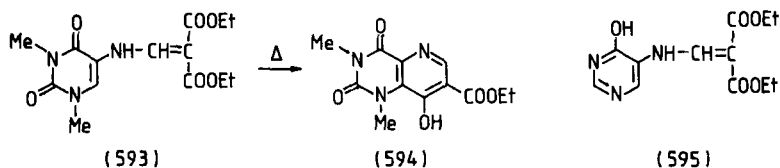


A bis(aminomethylenemalonate) derivative of pyridine (**170**) failed to cyclize when heated in Dowtherm A (59JA6297).

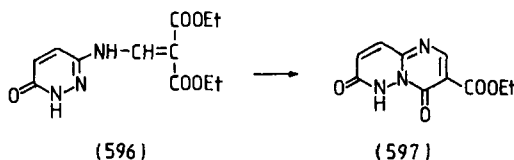
The heating of 5-pyrimidinylaminomethylenemalonates (**591** and **593**) in



Dowtherm A at 260–267°C for 6–60 min gave pyrido[3,2-*d*]pyrimidine-7-carboxylates (**592** and **594**) in 66–91% yields [67JCS(C)1745, 67USP332-0257], but *N*-(4-hydroxypyrimidin-5-yl)aminomethylenemalonate (**595**) failed to cyclize under similar conditions [67JCS(C)1745].

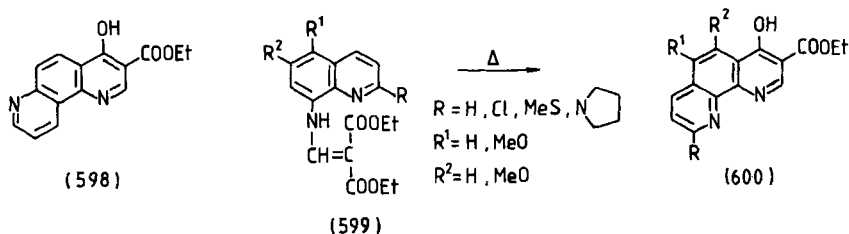


Pyrimido[1,2-*b*]pyridazinecarboxylate (**597**) was obtained in 32% yield on the cyclization of 3-pyridazinylaminomethylenemalonate (**596**) in Dowtherm A at 175°C for 100 min (88JHC1535).



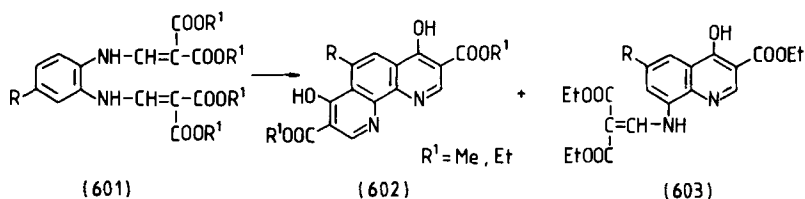
The ring closure of 5-quinolylaminomethylenemalonate in boiling diphenyl ether afforded 1,7-phenanthroline-3-carboxylate (**598**) in 98% yield (59MI3).

1,10-Phenanthroline-3-carboxylates (**600**) were obtained in good yields by the thermal cyclization of 8-quinolinylaminomethylenemalonates (**599**) [46JA1320; 59MI3; 62JOC3878; 74JAP(K)55698].



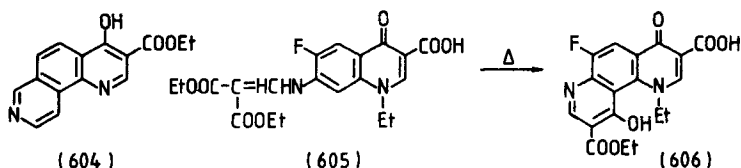
The ring closure of bis(aminomethylenemalonates) (**601**) by heating in boiling Dowtherm A (46JA1320) or in diphenyl ether (72GEP2220294) gave 1,10-phenanthroline-3,8-dicarboxylates (**602**, R = H, Me, Bu) in good yields. Cyclization (R = H, R¹ = Et) was also carried out in paraffin oil at 250 ± 5°C for 30 min (83JHC681).

It was later claimed that the thermal cyclization of bis(aminomethylenemalonates) (**601**, R = H, Me, Cl, NO₂, R¹ = Et) by heating in refluxing diphenyl ether for 15–30 min under nitrogen afforded 8-(substituted amino)quinoline-3-carboxylates (**603**) in 31–75% yields (78USP4123536). In the cases of the methyl and chloro derivatives (**601**, R = Me, Cl, R¹ = Et), 1,10-phenanthroline-3,8-dicarboxylates (**602**, R = Me, Cl, R¹ = Et) could also be isolated as byproducts in 3–4% yields.



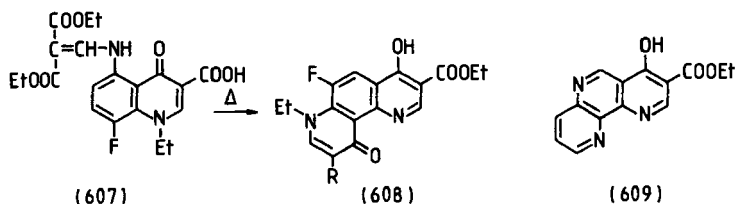
The cyclization of 5-isoquinolinylaminomethylenemalonate in boiling diphenyl ether for a few minutes afforded 1,8-phenanthroline-3-carboxylate (**604**) in 86% yield (83HCA620).

The thermal ring closure of *N*-(1-ethyl-4-oxo-1,4-dihydroquinolin-7-yl)aminomethylenemalonate (**605**) in diphenyl ether at 260°C for 1 hr afforded 1,7-phenanthroline-3,9-dicarboxylic acid 9-ethyl ester (**606**) in 23% yield (88USP4719302).



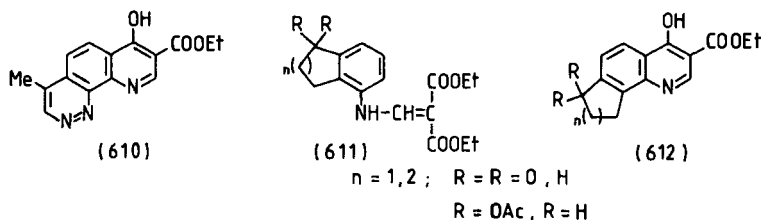
Thermal ring closure of *N*-(4-oxo-1,4-dihydroquinolinyl-5-yl)aminomethylenemalonate (**607**) gave a mixture of ethyl 1,7-phenanthroline-3-carboxylate (**608**, R = H) and 1,7-phenanthroline-3,9-dicarboxylic acid 3-ethyl ester (**608**, R = COOH) in 17% and 23% yields, respectively (88USP4719302).

Pyrido[3,2-*c*][1,5]naphthyridine-3-carboxylate (**609**) was prepared in 89% yield when diethyl *N*-(1,5-naphthyridin-4-yl)aminomethylenemalonate was refluxed in Dowtherm A for 1 hr (59JA6297).



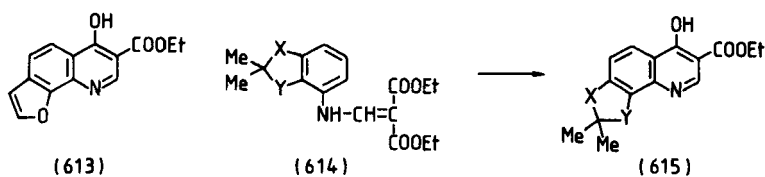
The cyclization of diethyl *N*-(4-methylcinnolin-8-yl)aminomethylenemalonate in diphenyl ether at 245°C for 20 min gave pyrido[3,2-*h*]cinnoline-8-carboxylate (**610**) in 31% yield (51JOC1414).

N-(2,3-Cycloalkanophenyl)aminomethylenemalonates (**611**) were cyclized to cycloalkano(*h*)quinoline-3-carboxylates (**612**) in good yields by heating in diphenyl ether (69SAP5212; 70GEP1912944; 73GEP2222818, 73GEP2222833).



Diethyl 7-benzofuranylaminomethylenemalonate afforded furo[3,2-*h*]quinoline-7-carboxylate (**613**) when heating in Dowtherm A for 0.5 hr (70GEP2021100; 71BRP1240446).

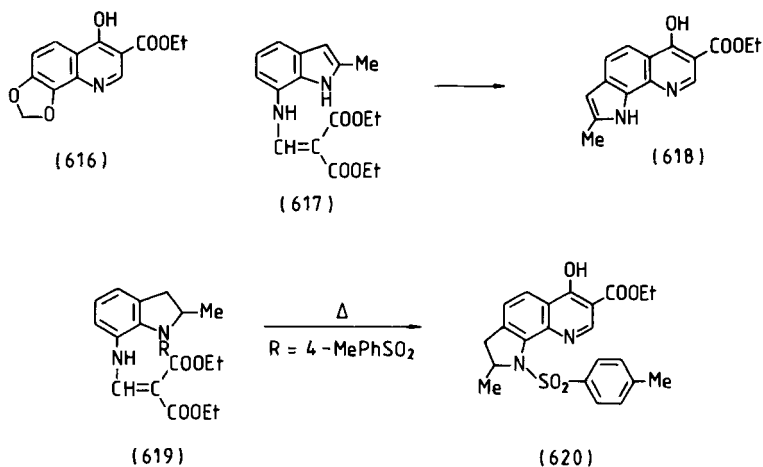
Isomeric 2,3-dihydrofuro[3,2-*h*]quinoline-7-carboxylate and 8,9-dihydrofuro[2,3-*h*]quinoline-3-carboxylate (**615**, $X = CH_2$, $Y = O$ and $X = O$, $Y = CH_2$) were prepared in good yields from *N*-(2,3-dihydrobenzofuran-7- and -5-yl)aminomethylenemalonates (**614**, $X = CH_2$, $Y = O$, and $X = O$, $Y = CH_2$), respectively, by thermal cyclization in boiling diphenyl ether (70JMC1110).



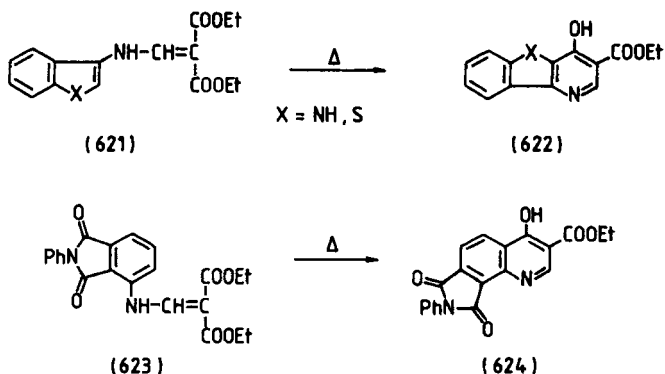
The cyclization of diethyl *N*-(2,3-methylenedioxyphenyl)aminomethylenemalonate in boiling diphenyl ether or Dowtherm A afforded 1,3-dioxo-

lo[*h*]quinolinecarboxylate (**616**) in good yield (69FRP2002888; 79JMC1354).

7-Indolylaminomethylenemalonate (**617**) was cyclized to pyrrolo[3,2-*h*]quinolinecarboxylate (**618**) in 54% yield by heating in diphenyl ether for 5 min. The dihydro derivative (**619**, R = H) failed to cyclize under similar conditions, but its *N*-(4-methylphenylsulfonyl) derivative (**619**, R = 4-MePhSO₂) gave the expected pyrrolo[3,2-*h*]quinoline carboxylate (**620**) in 44% yield [75JCS(P1)2409].

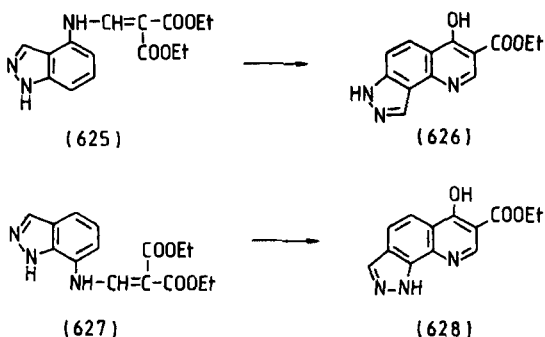


When heated in diphenyl ether at 240–254°C for 5–12 min, 3-indolyl- and 3-benzo(*b*)thienylaminomethylenemalonates (**621**, X = NH, S) gave pyrido[3,2-*b*]indolecarboxylate (**622**, X = NH) and benzo(*b*)thieno[3,2-*b*]pyridinecarboxylate (**622**, X = S) in 68–82% yields [76JAP(K)136698].

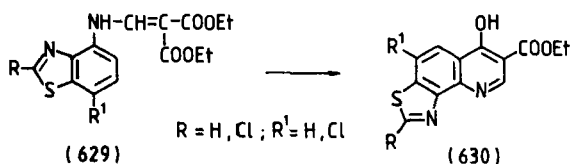


N-(1,3-Dioxoisindol-4-yl)aminomethylenemalonate (**623**) was cyclized to pyrrolo[3,4-*h*]quinoline-3-carboxylate (**624**) by heating in Dowtherm A (87MI1).

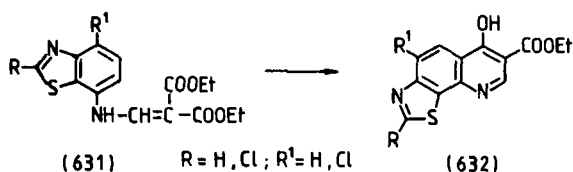
The isomeric pyrazolo[3,4-*h*]quinolinecarboxylate (**626**) and pyrazolo[4,3-*h*]quinolinecarboxylate (**628**) were prepared in 80% and 85% yields, respectively, on the cyclization of (4- and 7-indazolylamino)methylenemalonates (**625** and **627**) by heating in Gilotherm at 255°C for 10 min (78GEP2822214; 80MI3).



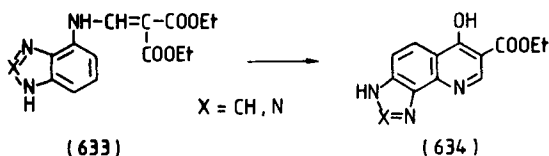
The thermal ring closure of 4-benzothiazolylaminomethylenemalonates (**629**) in boiling Dowtherm A for 10–30 min gave thiazolo[5,4-*h*]quinolinecarboxylates (**630**) in 61–78% yields [77JAP(K)83596, 77JAP(K)125196; 79CPB1].



The cyclization of 7-benzothiazolylaminomethylenemalonates (**631**) under similar conditions for 10–15 min afforded thiazolo[4,5-*h*]quinolinecarboxylates (**632**) in 77–100% yields [77JAP(K)83596, 77JAP(K)125196; 79CPB1].

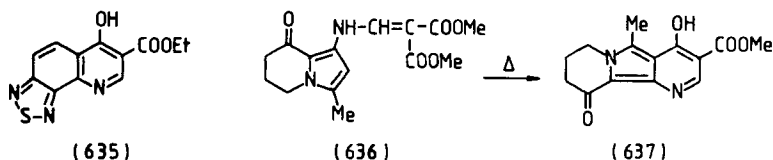


(Arylamino)methylenemalonates (**633**, X = CH, N) were cyclized to tricyclic products (**634**) in 65% and 98% yields, respectively, by heating in Dowtherm A at 250°C for 15 min (87CCC2918).



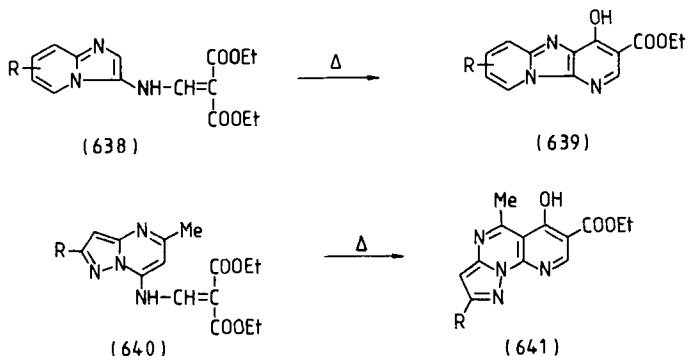
The thermal cyclization of *N*-(1,2,5-benzothiadiazol-4-yl)aminomethylenemalonate in diphenyl ether at 250–280°C gave 1,2,5-thiadiazolo[3,4-*h*]quinoline (**635**) in good yield (76KGS61; 84MI2).

Pyrido[2,3-*a*]indolizine-3-carboxylate (**637**) was obtained in 71% yield by the cyclization of (1-indolizinylamino)methylenemalonate (**636**) in boiling Dowtherm A for 40 min under argon (85JHC817).

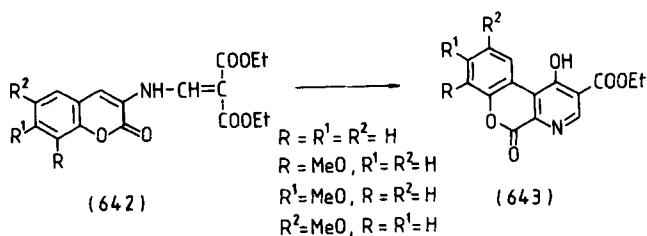


N-(3-Imidazo[1,2-*a*]pyridinyl)aminomethylenemalonates (**638**) were cyclized by heating in boiling Dowtherm A for 40 min to give dipyrido[1,2-*a* : 3',2'-*d*]imidazolecarboxylates (**639**) in 46–76% yields (81JHC1565).

N-(Pyrazolopyrimidin-7-yl)aminomethylenemalonates (**640**) were thermally cyclized when heated in diphenyl ether at 240°C for 7 min to give pyrazolopyridopyrimidinecarboxylates (**641**) in 73–75% yields (77GEP26 50780).

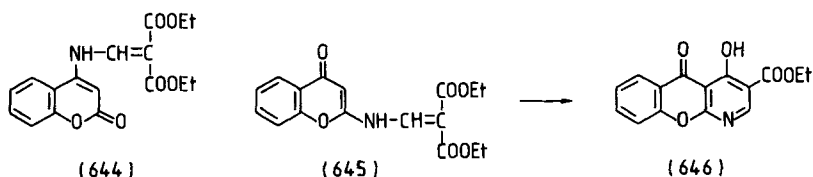


The cyclization of 3-coumarinylaminomethylenemalonates (**642**) in boiling Dowtherm A or diphenyl ether for 1.0–1.25 hr afforded benzopyrano[3,4-*b*]pyridinecarboxylates (**643**) in 77–79% yields (77JHC1009; 80USP4210758; 81JHC697).



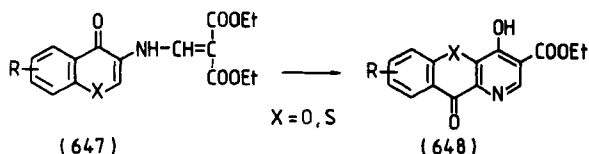
4-Coumarinylaminomethylenemalonate (**644**) failed to cyclize in boiling diphenyl ether (81JHC697).

2-Benzopyranylaminomethylenemalonate (**645**) was cyclized by heating in boiling diphenyl ether under nitrogen until the evolution of ethanol ceased. This reaction gave benzopyrano[2,3-*b*]pyridine (**646**) in 83% yield (78USP4117134; 81JCH697).

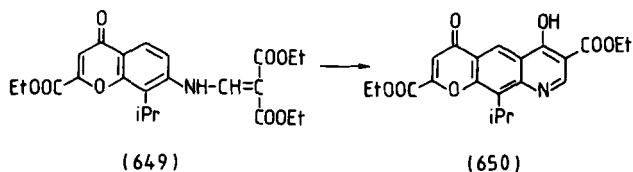


Under the previous conditions, 3-benzopyranylaminomethylenemalonates (**647**, $X = \text{O}$, $R = \text{H}$, 6-Me, 7-Cl) afforded benzopyrano[3,2-*b*]pyridines (**648**, $X = \text{O}$, $R = \text{H}$, 7-Me, 8-Cl) in 52–93% yields (78USP4066655; 81JHC697).

3-Benzothiopyranylaminomethylenemalonates (**647**, $X = \text{S}$, $R = \text{H}$, 6-Me, 8-Me) were cyclized in boiling diphenyl ether for 90 min under nitrogen to give benzothiopyrano[3,2-*b*]pyridine-3-carboxylates (**648**, $X = \text{S}$, $R = \text{H}$, 7-Me, 9-Me) in 89–92% yields (85JHC89).

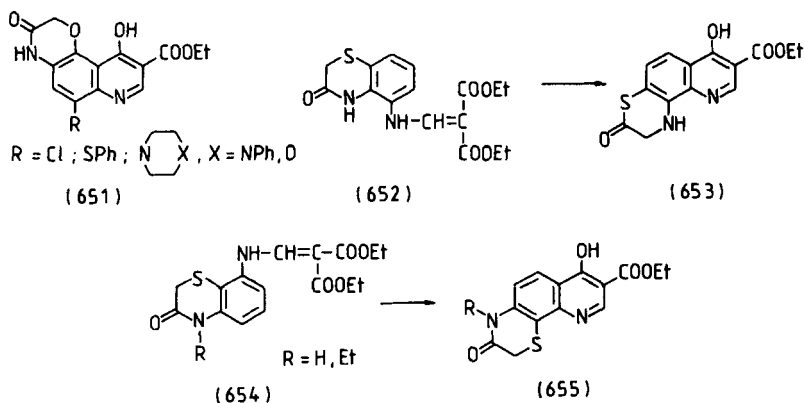


The cyclization of *N*-(8-isopropyl-7-benzopyranyl)aminomethylenemalonate (**649**) in boiling Dowtherm A for 1 hr afforded pyrano[3,2-*g*]-quinoline-2,7-decarboxylate (**650**) in 18% yield (80GEP2943658).

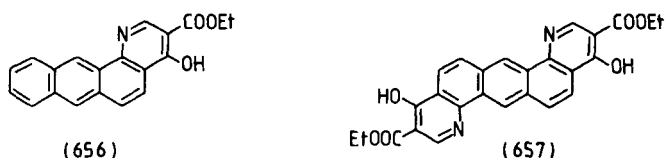


The cyclization of *N*-(1,4-benzoxazin-7-yl)aminomethylenemalonates (**82**) in boiling diphenyl ether for 30 min afforded 1,4-oxazino[2,3-*f*]quinoline-9-carboxylates (**651**) in 75–85% yields [88IJC(B)649].

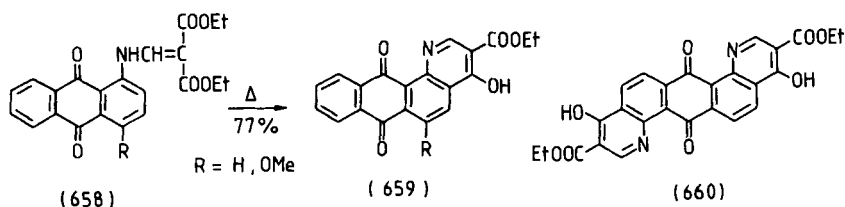
N-(1,4-Thiazin-5-yl)- and *N*-(1,4-thiazin-8-yl)aminomethylenemalonates (**652** and **654**) were cyclized in diphenyl ether at 250–270°C for 30 min to afford 1,4-thiazino[2,3-*h*]quinolinecarboxylate (**653**) and 1,4-thiazino[3,2-*h*]quinolinecarboxylates (**655**) in 86–90% yields, respectively (84M16).



The cyclization of 1-anthrylaminomethylenemalonate and 1,6-bis-(aminomethylenemalonate) (**189**) in boiling diphenyl ether gave tetracyclic (**656**) and pentacyclic derivatives (**657**) in 90% and 83% yields, respectively (62M12).

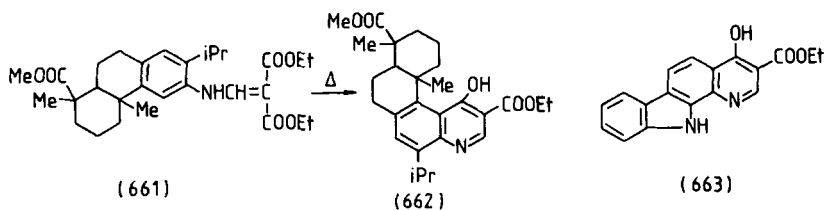


1-Anthraquinonylaminomethylenemalonates (**658**, R = H, OMe) and 1,5-bis(aminomethylenemalonate) (**191**) in boiling diphenyl ether readily gave tetracyclic and pentacyclic pyridine derivatives (**659** and **660**) in good yields (59MI2). At the same time, the thermal cyclization of the 4-hydroxy derivative (**658**, R = OH) and 1,4-bis(aminomethylenemalonate) [**658**, R = —NHCH=C(COOEt)₂] did not yield the expected condensed tetracyclic pyridine derivatives.



The cyclization of *N*-(octahydrophenanthronyl)aminomethylenemalonate (**661**) in boiling Dowtherm A gave octahydronaphtho[1,2-*f*]quinolinecarboxylate (**662**) (54JPJ203).

Pyrido[2,3-*a*]carbazole-3-carboxylate (**663**) was prepared in good yield by the cyclization of (1-carbazolylamino)methylenemalonate in boiling diphenyl ether (52JOC1501).

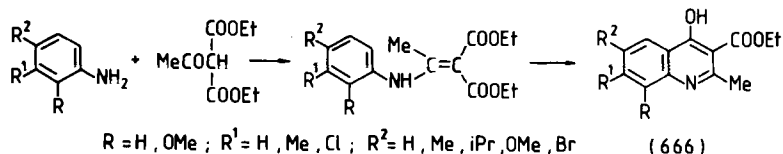


The thermal ring closure of *N*-(1,2,3,4-tetrahydrodibenzofuran-8-yl)-aminomethylenemalonate (**664**) in boiling Dowtherm A for 30 min afforded 7,8,9,10-tetrahydrobenzofuro[3,2-*h*]quinoline-3-carboxylate (**665**) in good yield (69GEP1908542; 70GEP2021100; 71BRP1240446).



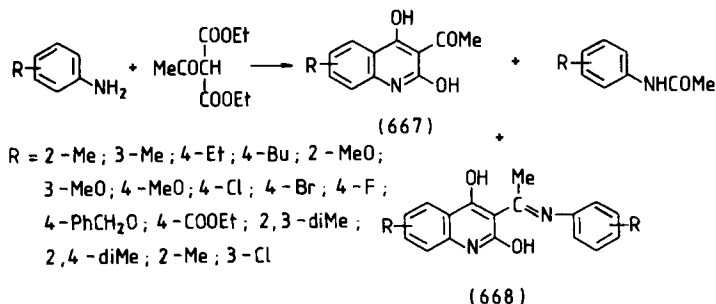
Diethyl 1-(phenylamino)ethylidenemalonate was smoothly cyclized to ethyl 2-methylquinoline-3-carboxylate (**666**, $R = R^1 = R^2 = H$) in moderate yield by heating in mineral oil at 250°C (39JA2890) or in Dowtherm A at 210–225°C for 30 min (81CPB3712).

Diethyl acetylmalonate was reacted with anilines in benzene in the presence of a catalytic amount of concentrated hydrochloric acid at 65–70°C for 16 hr. Then, after evaporation, the residues were heated at 195–220°C for 5–15 min to give 2-methylquinoline-3-carboxylates (**666**) in 36–80% yields (83KGS1521). Meta-substituted anilines ($R = Me, Cl$) gave 7-substituted 2-methylquinoline-3-carboxylates.



The reactions of anilines and diethyl acetylmalonate in 1-chloronaphthalene at 220–235°C for 1.5 hr afforded a mixture of 3-acetyl-2,4-dihydroxyquinolines (**667**) and acetanilides, and if the reaction mixtures were heated above 240°C, an additional product (**668**) was formed (81M13). From the reaction mixtures, 3-acetylquinolinones were isolated in 9–42% yields.

The reactions of anilines ($R = 4-MeO$ and $3-Cl$) and diethyl acetylmalonate in nitrobenzene at 230–235°C for 1–2 hr gave 2,4-dihydroxy-3-acetylquinolines (**667**, $R = 6-MeO$ and $7-Cl$). In the case of 3-chloroaniline, a mixture of the isomeric 5- and 7-chloroquinolines was obtained (46JA324). The 7-chloroquinoline was the major isomer.

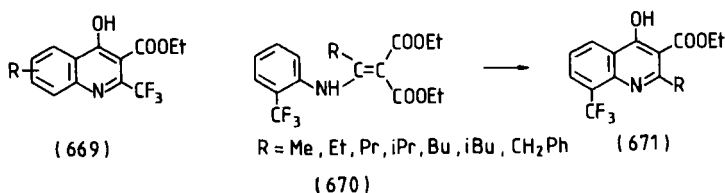


The heating of 2,2,2-trifluoro-1-(arylamino)ethylidenemalonates (**321**) at 210–250°C gave 2-trifluoromethylquinoline-3-carboxylates (**669**) in 48–99% yields (80EUP12639).

1-[(2-Trifluoromethylphenyl)amino]alkylidenemalonates (**670**) were cyclized to 2-substituted quinoline-3-carboxylates (**671**) in 32–70% yields by heating in diphenyl ether at 240°C (77GEP2705446; 78FRP2377400).

Dimethyl methylthio(phenylamino)methylenemalonate was cyclized in boiling decalin for 2 hr to afford methyl 2-methylthio-4-hydroxyquinoline-3-carboxylate in 70% yield (69T4649).

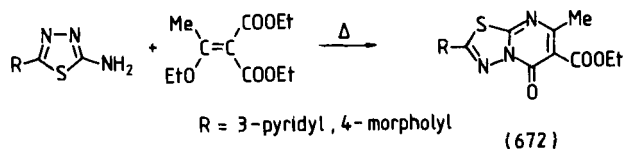
A solution of diethyl (2,3,4-trifluorophenylamino)(*p*-methoxybenzylthio)methylenemalonate in diphenyl ether was added to diphenyl ether at 110°C, and the reaction mixture was then stirred at 250–260°C for 20 min under nitrogen to give ethyl 4-hydroxy-2-(*p*-methoxyphenylthio)-6,7,8-trifluoroquinoline-3-carboxylate in 82% yield (88EUP286089).



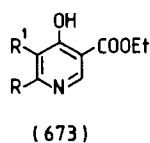
Dimethyl methylthio(2-trifluoromethylphenylamino)methylenemalonate (**670**, R = MeS) was cyclized by heating at 180°C for 30 min to afford 2-methylthioquinoline-3-carboxylate (**671**, R = MeS) in 71% yield (84FRP2532939).

The reactions of 2-amino-1,3,4-thiadiazoles and diethyl 1-ethoxyethylidenemalonate in diglyme at 140°C for 20 hr gave 7-methyl-1,3,4-thiadiazolo[3,2-*a*]pyrimidine-6-carboxylates (**672**) in 14–25% yields after column chromatography (86FES737). Reactions in ethanol or dimethylacetamide were unsuccessful.

The cyclization of aminomethylenemalonates (**275**) in Dowtherm A at 250–260°C for 5–90 min, sometimes under nitrogen or argon, gave mono-



and bicyclic pyridine-3-carboxylates (**673**) in 30–88% yields [75JHC1245; 77JHC477; 78JAP(K)63382; 88EUP270494]. The ring closure of *N*-(2-methylcyclohexen-1-yl)aminomethylenemalonate (**674**) under similar conditions afforded 4*a*-methylhexahydroquinoline-3-carboxylate (**675**) in 50% yield (75JHC1245). The acidic cyclization of aminomethylenemalonates (**275**, $R, R^1 = -(CH_2)_4-$ and $R = Me, R^1 = COOEt$) in polyphosphoric acid, polyphosphate ester, or phosphoryl chloride gave only intractable materials (75JHC1245).



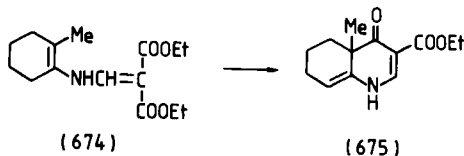
R and $R^1 = Me, Ph$

$R = H, R^1 = COOMe$

$R = Me, R^1 = COMe, COOMe, COOEt, SO_2C_6H_4-4Me$

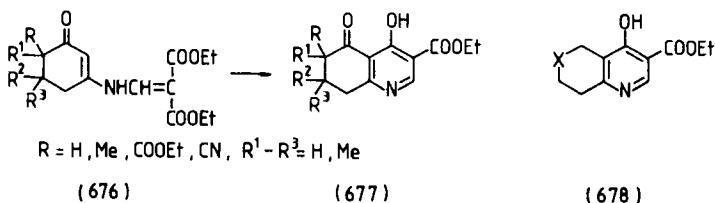
$R = R^1 = -(CH_2)_2CO-$

$R = R^1 = -(CH_2)_n-, n = 3-6, 8, 9$

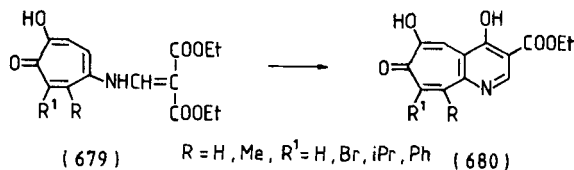


The thermal cyclization of *N*-(3-oxocyclohexen-1-yl)aminomethylenemalonates (**676**) in diphenyl ether at 240–260°C afforded tetrahydroquinoline-3-carboxylates (**677**) in good yields [79JAP(K)119484; 80GEP2947948, 80GEP3008884; 82JAP(K)116048, 82JHC289].

The ring closure of aminomethylenemalonates (**278**) in Dowtherm A at 240°C for 0.5 hr under nitrogen afforded the corresponding condensed pyridine-3-carboxylates (**678**, X as in **278**) (86EUP168350; 87USP4647566).



5-Cycloheptatrienylaminomethylenemalonates (**679**) yielded condensed pyridinecarboxylates (**680**) when heated in Dowtherm A for 0.5 hr (55BRP723341; 59NKZ75; 60NKZ295; 68NKZ620).

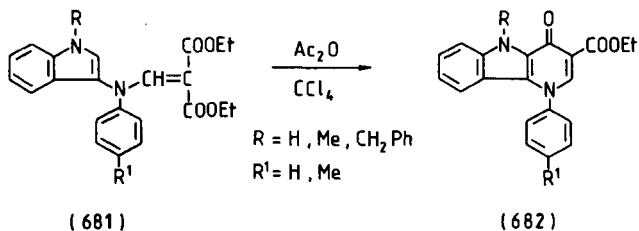


2. UNDER ACIDIC CONDITIONS

In the cyclization of *N*-(het)arylaminomethylenemalonates, a wide variety of acidic agents have been used. Under such circumstances, not only *N*-mono but also *N,N*-disubstituted derivatives could readily be cyclized.

When diethyl phenyl(phenylamino)methylenemalonate (**4**) was dissolved in concentrated sulfuric acid and the solution was kept at ambient temperature for a few days, 2-phenyl-4-hydroxyquinoline-3-carboxylic acid was obtained on the dilution of the reaction mixture with water (36JCS428).

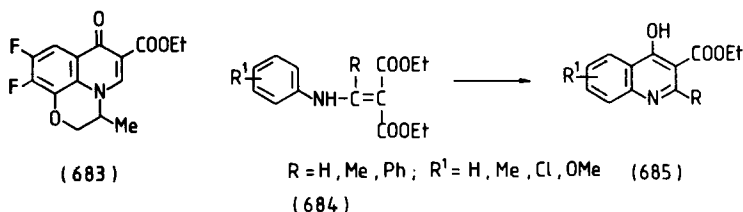
3-Indolylaminomethylenemalonates (**681**) were regioselectively cyclized on the action of acetic anhydride or trifluoroacetic anhydride in carbon tetrachloride at 10–20°C for 3 hr, to give δ -carboline (**682**) in 22–75% yields (85ZOR432).



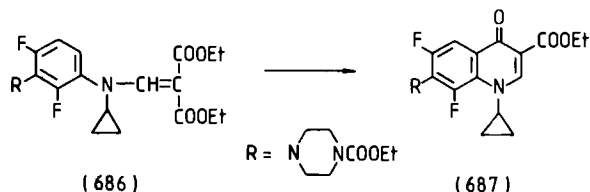
Pyrido[1,2,3-*de*]-1,4-benzoxazine-6-carboxylate (**683**) was prepared in 96% yield by the cyclization of (1,4-benzoxazin-4-yl)methylenemalonate (**272**) on the action of a mixture of acetic anhydride and concentrated sulfuric acid at room temperature [84JAP(K)122493], or in 58–94% yields by heating in a mixture of acyl halides and concentrated sulfuric acid at 80–110°C for 1 hr [84JAP(K)216890], or in 75% yields by heating in

polyphosphate at 140–150°C for 1.5 hr [86JAP(K)246172, 86JAP(K)2461188]. Optically active 3*S*-methyl-9,10-difluoropyrido[1,2,3-*de*]-1,4-benzoxazine-6-carboxylate (**683**) was obtained in 70–76% yields on the cyclization of optically active (3*S*-methyl-7,8-difluoro-1,4-benzoxazin-4-yl)methylenemalonate (**272**) by heating in a 2 : 1 mixture of acetic anhydride and concentrated sulfuric acid at room temperature for 1 hr and then at 50–60°C for 30–40 min (86EUP206283; 88EUP273399).

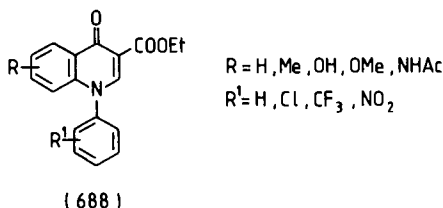
Diethyl (arylamino)methylenemalonates (**684**) were cyclized with a 2 : 1 mixture of acetic anhydride and concentrated sulfuric acid at ambient temperature to give 4-hydroxyquinoline-3-carboxylates (**685**) in 15–80% yields (54JIC555, 54JIC711, 54JIC951).



The ring closure of *N*-cyclopropyl-*N*-(trisubstituted phenyl)aminomethylenemalonate (**686**) was carried out in a mixture of acetic anhydride and concentrated sulfuric acid to give 1-cyclopropylquinoline-3-carboxylate (**687**) in 41% yield (85NKK2054). When the cyclization was carried out in polyphosphoric acid at 100–110°C for 30 min, 1-cyclopropylquinoline-3-carboxylate (**687**) was obtained in 44% yield [86JAP(K)143364].



The cyclization of (*N,N*-diarylamino)methylenemalonates (**112**) in a 2 : 1 mixture of acetic anhydride and concentrated sulfuric acid at room temperature for 5–15 min gave 1-phenyl-4-oxo-1,4-dihydroquinoline-3-carboxylates (**688**) in good yields (69BRP1147336). The regioselective cyclization of unsymmetrically substituted *N,N*-diarylaminomethylenemalonates (**112**, R ≠ R¹) took place on that phenyl ring that contained an electron-donating group (e.g., Me, OH, MeO, NHAc) or that did not bear an electron-withdrawing group (e.g., CF₃, NO₂, Cl).

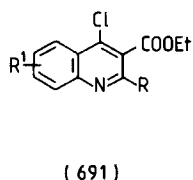
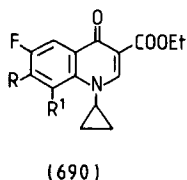
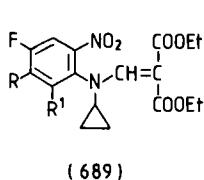


As cyclization with a mixture of acetic anhydride and concentrated sulfuric acid occurred very vigorously in the initial stage of the reaction, Agui *et al.* did not recommend it for large-scale operations (75JHC557). Renault *et al.* experienced that the yield of cyclization product decreased dramatically on scaling-up (76MI3).

The cyclization of *N*-(bromophenyl)aminomethylenemalonates (**684**, R = H, R¹ = Br) in a mixture of acetic acid and concentrated sulfuric acid afforded quinoline-3-carboxylic acids in poor yields due to the decomposition of the starting *N*-(bromophenyl)aminomethylenemalonates (78JIC193).

N-Cyclopropyl-*N*-(2,3-disubstituted 4-fluoro-6-nitrophenyl)aminomethylenemalonates (**689**) were cyclized to 1-cyclopropylquinoline-3-carboxylates (**690**) in a mixture of acetic anhydride and concentrated sulfuric acid at 50–70°C in 29–66% yields [86JAP(K)143363; 87NEP471; 88EUP287951; 89USP4874764].

Arylaminomethylenemalonates (**684**) were cyclized by heating in phosphoryl chloride; depending on the work-up process, either the primarily formed 4-chloroquinoline-3-carboxylates (**691**) (e.g., 66BEP670520, 66NEP447; 68FRP1531495; 69GEP1814187; 70FRP7611; 71GEP2033971, 71JHC357; 72S625; 77TL4545) or their hydrolytic products, 4-hydroxyquinoline-3-carboxylates (**685**) (e.g., 36JCS428; 66NEP447; 68BRP1120870, 68FRP1531495, 68SAP5655; 69BRP1168105; 70FRP7975) were obtained in good yields. The ring closure was sometimes carried out in a solvent (e.g., dioxane, 69BRP1168105).



The ring closure of diethyl *N*-(4-cycloheptylphenyl)aminomethylenemalonate in boiling phosphoryl chloride in the presence of a cata-

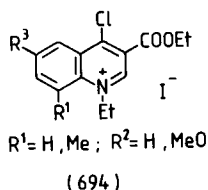
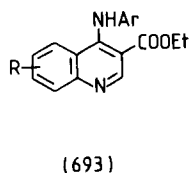
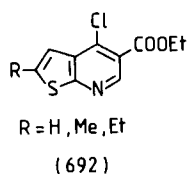
lytic amount of polyphosphoric acid for 2 hr afforded 6-cycloheptyl-4-chloroquinoline-3-carboxylate (**691**, $R = H$, $R^1 = 6\text{-cycloheptyl}$) (74GEP-2421121).

N-Ethyl-*N*-(2,5-dimethoxyphenyl)aminomethylenemalonate was treated with phosphoryl chloride in boiling chloroform for 3 hr, to give ethyl 1-ethyl-5,8-dimethoxy-4-oxo-1,4-dihydroquinoline-3-carboxylate in 69% yield (82HCA2645).

4-Chlorothieno[2,3-*b*]pyridine-5-carboxylate (**692**, $R = H$) was prepared in 67% yield by the cyclization of 2-thienylaminomethylenemalonate (**582**, $R = R^1 = R^2 = H$) in boiling phosphoryl chloride for 2 hr (76GEP2447477). 5-Alkyl derivatives of compound (**582**, $R = \text{Me, Et}$, $R^1 = R^2 = H$) gave 2-alkyl-4-chlorothieno[2,3-*b*]pyridide-5-carboxylates (**692**, $R = \text{Me, Et}$) in 42–55% yields when reacted under similar conditions for 4 hr (80MI4; 84EUP126970).

4-(Arylamino)quinoline-3-carboxylates (**693**) were prepared by the cyclization of *N'*-aryl(arylamino)methylenemalonamates (**252**) on the action of phosphoryl chloride in boiling benzene or of phosphorus pentoxide in refluxing xylene (46JA1246). Phosphoryl chloride proved to be a more effective cyclization agent than phosphorus pentoxide. This method could not be applied for the preparation of 4-alkylaminoquinoline-5-carboxylates.

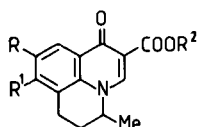
Diethyl *N*-ethyl-*N*-arylaminomethylenemalonates (**106**, $R = \text{Et}$, $R^2 = H$) were heated in phosphoryl chloride at 95–105°C for 3 hr to give quinolinium derivatives, which were isolated as iodide salts (**694**) [74JAP(K)32933].



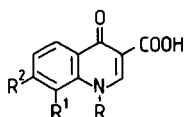
The heating of *N*-ethyl-*N*-(3,4-methylenedioxyphenyl)aminomethylenemalonate (**286**) in boiling phosphoryl chloride for 3 hr gave oxolinic acid in 35% yield after the work-up process (87KFZ1249).

Diethyl (5-cyano-2-methyltetrahydroquinolin-1-yl)methylenemalonate (**130**, $R = H$, $R^1 = \text{CN}$) was heated in boiling phosphoryl chloride for 4 hr to give 8-cyano-5-methylbenzo[*i*]quinolizine-2-carboxylic acid (**695**, $R = H$, $R^1 = \text{CN}$, $R^2 = H$) in 69% yield after the work-up process (86USP4565872).

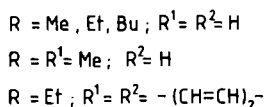
A solution of (2,5-dimethyl-6-fluorotetrahydroquinolin-1-yl)methylene-malonate (**130**, R = F, R¹ = Me) in toluene was added to boiling phosphoryl chloride over a period of 2 hr, and the reaction mixture was then refluxed for another 1.5 hr to afford benzo[*j*]quinolizine-2-carboxylate (**695**, R = F, R¹ = Me, R² = Et) in 77% yield (87EUP245913).



(695)

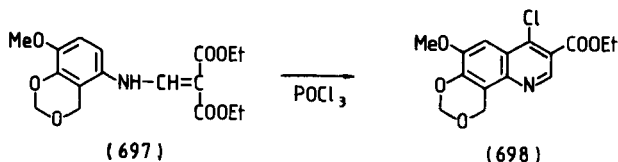


(696)



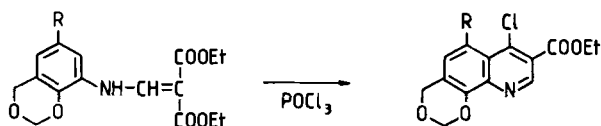
Markees and Schwab cyclized *N*-alkyl-*N*-arylaminomethylenemalonates (**106**, R³ = H) by treatment with phosphorus pentoxide (72HCA1319). Equal amounts of aminomethylenemalonates (**106**, R³ = H) and phosphorus pentoxide were warmed to about 130°C, when exothermic reactions occurred. The temperature of the reaction mixtures rose to about 190°C. After the work-up process, quinoline-3-carboxylic acids (**696**) were obtained in 41–63% yields. Better yields (76–96%) were achieved when the reactions were carried out in nitrobenzene.

The isomeric 1,3-dioxino[4,5-*h*]quinoline (**698**) and 1,3-dioxino[5,4-*h*]quinoline (**700**, R = Me) were prepared by cyclization of the appropriate *N*-(1,3-benzodioxanyl)aminomethylenemalonates (**697** and **699**, R = Me) in boiling phosphoryl chloride for 12 hr (72MI5). While the methyl derivative of compound **699** (R = Me) readily gave 1,3-dioxino[5,4-*h*]quinoline (**700**, R = Me), the unsubstituted and chloro derivatives (**699**, R = H, Cl) could not be cyclized by heating in phosphorus chloride, even if triethylamine, SnCl₄, or PCl₅ was also present (72MI5).



(697)

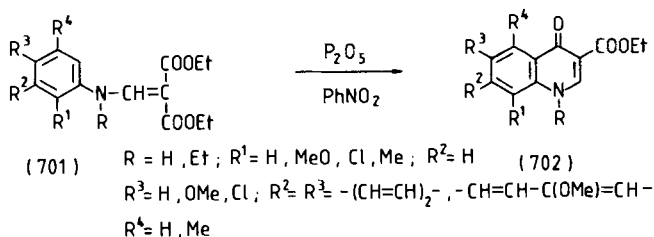
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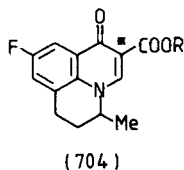
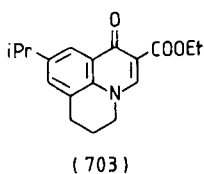
The cyclization of arylaminomethylenemalonates (**701**) on the action of phosphorus pentoxide in nitrobenzene gave quinoline-3-carboxylates (**702**) in 16–85% yields (74JMC137). Polyphosphoric acid proved to be a more effective cyclization agent than the phosphorus pentoxide-nitrobenzene system. For example, a chloro derivative (**701**, $R = Et$, $R^1 = Cl$, $R^2 = R^3 = R^4 = H$) gave quinoline-3-carboxylate (**702**, $R = Et$, $R^1 = Cl$, $R^2 = R^3 = R^4 = H$) in 46% yield on the action of polyphosphoric acid, whereas the yield was only 16% in the phosphorus pentoxide-nitrobenzene system.



The ring closure of (6-isopropyl-1,2,3,4-tetrahydroquinolin-1-yl)methylenemalonate (**127**, $R = R^2 = H$, $R^1 = iPr$) by heating in phosphoric acid at $100^\circ C$ for 1 hr gave the benzo[*i,j*]quinolizinecarboxylate (**703**) in 54% yield (74GEP2415763).

A mixture of diethyl phenylaminomethylenemalonate (30 mmol) and triethyl phosphate (100 mmol) was heated at $220-225^\circ C$ for 1 hr, and the reaction was then hydrolyzed with aqueous sodium hydroxide to give 1-ethyl-4-oxo-1,4-dihydroquinoline-3-carboxylic acid in 80% yield. 6,7-Methylenedioxyquinolinecarboxylic acid (oxolinic acid) was prepared in 75% yield in a similar way. This product was also obtained in the reaction of 3,4-methylenedioxyaniline, EMME, and triethyl phosphate under similar conditions (70MIP1).

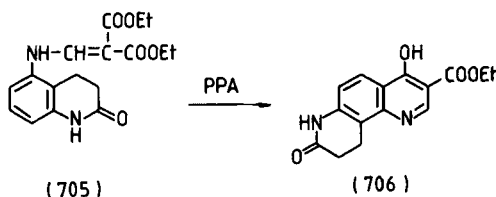
Flumequine (**704**, $R = H$) was prepared in 91% yield by the cyclization of diethyl (6-fluoro-2-methyltetrahydroquinolin-1-yl)methylenemalonate (**130**, $R = F$, $R^1 = H$) in boiling toluene in the presence of tetraphosphoric acid for 2 hr, or in the presence of polyphosphoric acid for 14 hr. The



tricyclic ester (**704**, R = Et) was then hydrolyzed to the carboxylic acid (**704**, R = H) (81FRP2476079).

¹⁴C-Flumequine (**704**, R = H, *) was obtained from ¹⁴C-labeled (6-fluoro-2-methyltetrahydroquinolin-1-yl)methylenemalonate (**130**, R = F, R¹ = H) by treatment in polyphosphoric acid at 130°C for 75 min (86MI14).

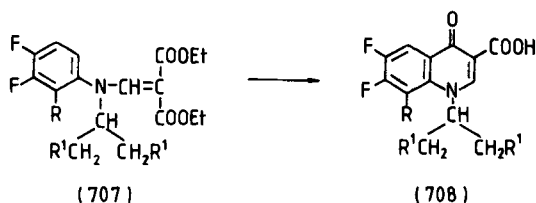
The ring closure of *N*-(2-oxo-1,2,3,4-tetrahydroquinolin-5-yl)amino-methylenemalonate (**705**) by heating in polyphosphoric acid at 140°C for 30 min gave 1,7-phenanthrolinecarboxylate (**706**) in good yield [80JAP(K)69582].



1-Alkylquinoline-3-carboxylic acids (**696**, R = Et, Pr, R¹ = R² = Me) were prepared in 37–59% yields by the cyclization of *N*-alkyl-*N*-(2,3-dimethylphenyl)aminomethylenemalonates (**106**, R = Et, Pr, R¹ = R² = Me, R³ = H) in polyphosphoric acid at 150°C for 1 hr, followed by a work-up process using aqueous sodium hydroxide in dioxane (74GEP2246503).

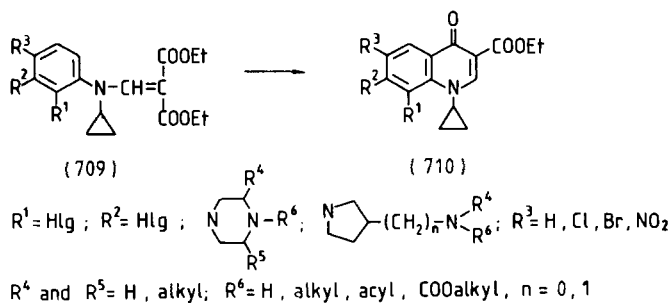
N-Ethyl-*N*-(3-halo-2-methylphenyl)aminomethylenemalonates (**106**, R = Et, R¹ = Me, R² = Hlg, R³ = H) were heated in polyphosphoric acid, prepared from phosphoric acid and phosphorus pentoxide, at 140°C for 40 min. The reaction mixture was then poured into water, and the product was hydrolyzed with 10% aqueous sodium hydroxide to give quinoline-3-carboxylic acids (**696**, R = Et, R¹ = Me, R² = Hlg) in 68–70% yields (80GEP3007006).

The cyclization of *N*-isopropyl-*N*-(2,3,4-trifluorophenyl)aminomethylenemalonate (**707**, R = F; R¹ = H) by heating in polyphosphoric acid at 80–130°C for 1 hr gave 1-isopropylquinoline-3-carboxylic acid (**708**, R = F, R¹ = H) in 20% yield (85GEP3433924).

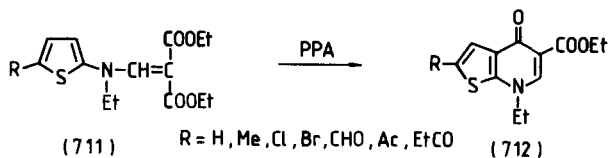


N-Cyclopropyl-*N*-(2,3,4-trihalophenyl)aminomethylenemalonates (**707**, R = Cl, F; R¹ = valence bond) were cyclized by heating in polyphosphoric acid at 120–135°C for 1–3 hr to afford 1-cyclopropylquinoline-3-carboxylates (**708**, R = Cl, F; R¹ = valence bond) in 13–49% yields (84BEP899399; 85SAP3954; 85EUP183129, 86EUP195316).

The ring closure of *N*-cyclopropyl-*N*-(2,3,4-trisubstituted phenyl)aminomethylenemalonates (**709**) in polyphosphoric acid at 120–130°C gave 1-cyclopropylquinoline-3-carboxylates (**710**) in moderate yields [87JAP(K)26272].

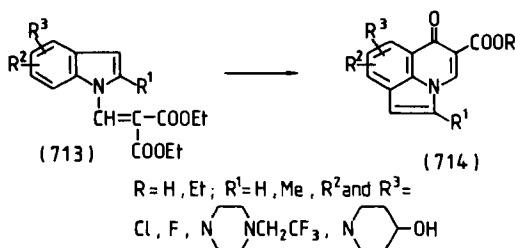


N-Ethyl-*N*-(5-substituted 2-thienyl)aminomethylenemalonates (**711**) were cyclized by heating in polyphosphoric acid at 110–120°C for 20–30 min to afford 7-ethyl-4-oxothieno[2,3-*b*]pyridine-5-carboxylates (**712**) in 65–80% yields (85EUP161235; 87MI3; 88MI12).



Depending on the work-up conditions, pyrrolo[3,2,1-*ij*]quinoline-carboxylic acids (**714**, R = H) [78JAP(K)82799; 79GEP2914218; 79GEP2914258; 80JAP(K)145612, 80JAP(K)149284; 82BEP891046, 82BEP891537; 83JAP(K)90511] or pyrrolo[3,2,1-*ij*]quinolinecarboxylates (**714**, R = Et) [75USP3917609; 83JAP(K)13585; 88JHC1567] were prepared in moderate to good yields on the cyclization of 1-indolylmethylenemalonates (**713**) by heating in polyphosphoric acid at 40°C (88JHC1567) or at 120–180°C for 20–60 min.

N-(1,2,3,4-Tetrahydroquinolin-1-yl)aminomethylenemalonates (**715**) were heated in polyphosphoric acid at 100–160°C for 5–90 min to give

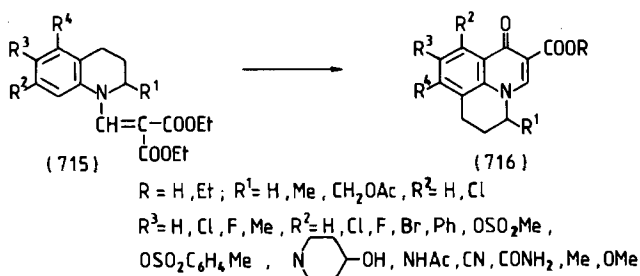


benzo[*ij*]quinolizinecarboxylates (**716**, R = Et), which were isolated as esters (R = Et) or as acids (R = H) [79GEP2914218, 79GEP2914258; 80JAP(K)38364, 80JAP(K)145612, 80JAP(K)149284; 81BEP885605, 81FRP2463771, 81JAP(K)55388, 81JAP(K)59773; 82BEP891046, 82BEP891537; 83EUP79162, 83JAP(K)90511, 83USP4380543, 83USP4404207, 83USP4416884; 84EUP101829, 84EUP109284, 84EUP109285, 84EUP119779, 84NEP1115, 84USP4443447; 86USP4565872]. Under the reaction circumstances, the cyano group ($\text{R}^4 = \text{CN}$) was partially hydrolyzed to the carboxamido group ($\text{R}^4 = \text{CONH}_2$) (83EUP79162; 86USP4565872).

Optically active benzo[*ij*]quinolizine-2-carboxylic acid (**716**, R = R² = H, R¹ = Me, R³ = F, R⁴ = Br) was prepared in the reaction of optically active 2-methyl-5-bromo-6-fluoro-1,2,3,4-tetrahydroquinoline and EMME in polyphosphoric acid [88JAP(K)192753].

The tetrahydroquinolines were reacted with EMME at 150°C for 1 hr and then cyclized in polyphosphoric acid at 150°C for 30 min. The tricyclic ester (**716**, R = Et, R¹ = H, Me; R² = H; R³ = H, F, Cl, Br; R⁴ = F, Cl, 4-methyl-1-piperazinyl) were hydrolyzed with concentrated hydrochloric acid in 90% acetic acid to afford the corresponding acids (**716**, R = H) in 58–78% yields (89CPB2103).

Diethyl (5-acetamido-6-fluor-2-methyl-1,2,3,4-tetrahydroquinolin-1-yl)-methylenemalonate (**130**, R = F, R¹ = NHAc) was cyclized by heating



in polyphosphoric acid at 100°C for 45 min. The resulting 8-acetamido-9-fluorobenzo[*ij*]quinolizine-2-carboxylate (**695**, R = F, R¹ = NHAc, R² = Et) was hydrolyzed with aqueous sodium hydroxide to 8-amino-9-fluorobenzo[*ij*]quinolizine-2-carboxylic acid (**695**, R = F, R¹ = NH₂, R² = H) (85USP4524148).

The optically active enantiomers of ethyl benzo[*ij*]quinolizine-2-carboxylates (**695**, R = F, R¹ = Me, R² = Et) were prepared in 65% yields by cyclization of the enantiomers of (tetrahydroquinolin-1-yl)methylenemalonates (**130**, R = F, R¹ = Me) in polyphosphoric acid at 100°C for 30 min (87JMC839). The 5-desmethyl derivative of **695** (R = F, R¹ = Me, R² = Et) was prepared similarly.

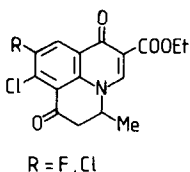
(4-Oxotetrahydroquinolin-1-yl)methylenemalonates (**132**) were heated in polyphosphoric acid at 110–120°C for 2 hr to give 1,7-dioxobenzo[*i,j*]quinoline-2-carboxylates (**717**) in 82–85% yields (86EUP203795).

The ring closure of (1,4-benzoxazin-4-yl)methylenemalonates (**136**) by heating in polyphosphoric acid at 100–150°C for 0.5–1 hr afforded ethyl pyrido[1,2,3-*de*]-1,4-benzoxazine-6-carboxylates (**718**, R³ = Et) in moderate or good yields [75USP3883522; 84USP4443447; 86EUP184384; 88JAP(K)60990]. The cyclizations were sometimes carried out under nitrogen (86EUP1843484).

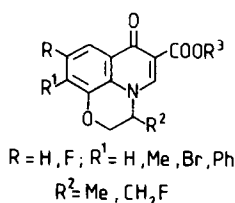
The cyclization of (8-acetyl-7-fluoro-3-methyl-1,4-benzoxazin-4-yl)methylenemalonate (**136**, R = F, R¹ = Ac, R² = Me) by heating in polyphosphoric acid at 65°C for 2 hr gave 10-acetyl-9-fluoro-5-methylpyrido[1,2,3-*de*]-1,4-benzoxazine-6-carboxylic acid (**718**, R = F, R¹ = Ac, R² = Me, R³ = H) in 63% yield (87JHC1509).

(1,4-Benzothiazin-4-yl)methylenemalonates (**141**) were cyclized by heating in polyphosphoric acid at 160–185°C for 1 hr to afford pyrido[1,2,3-*de*]-1,4-benzothiazine-6-carboxylates or carboxylic acids (**719**, R⁴ = Et, H) in 37–68% yields after the work-up processes [85JAP(K)208987; 87JMC465; 88EUP252352, 88EUP267432].

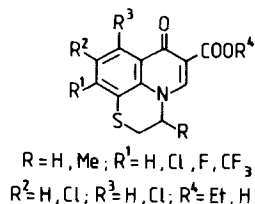
Racemic and optically active ethyl 3-methylpyrido[1,2,3-*de*]quinoxaline-6-carboxylates (**721**) were prepared on the cyclization of diethyl



(717)

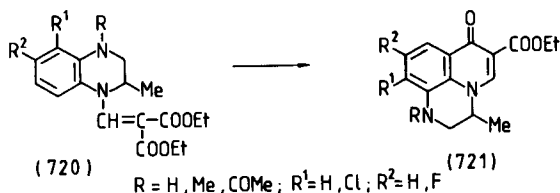


(718)



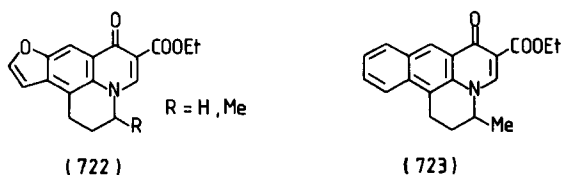
(719)

(2-methyltetrahydroquinoxalin-1-yl)methylenemalonates (**720**) by heating in polyphosphoric acid at 110–120°C for 45 min under nitrogen (82USP4348521).

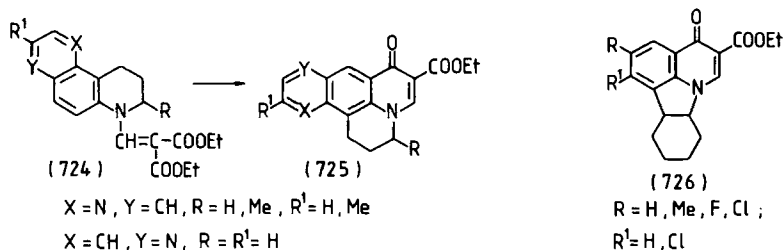


Diethyl (furo[3,2-*f*]quinolin-6-yl)methylenemalonates (**152**) were cyclized by heating in polyphosphoric acid at 120°C for 20 min to give tetracyclic benzofuro[4,5,6-*ij*]quinolizinecarboxylates (**722**) in 47–49% yields (84CPB4923).

The ring closure of diethyl (benzo[*f*]quinolin-1-yl)methylenemalonate (**148**) was carried out by heating in polyphosphoric acid at 90–110°C to give ethyl naphtho[1,2,3-*ij*]quinolizine-6-carboxylate (**723**) (84USP4456606).



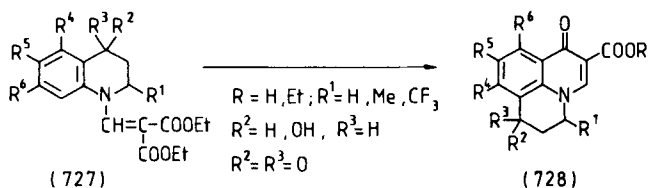
The ring closure of *N*-(1,7-phenanthrolin-7-yl)- and *N*-(4,7-phenanthrolin-7-yl)aminomethylenemalonates (**724**, $\text{X} = \text{N}$, $\text{Y} = \text{CH}$ and $\text{X} = \text{CH}$, $\text{Y} = \text{N}$) by heating in polyphosphoric acid at 110–120°C for 11 min afforded tetracyclic ring systems (**725**) in 54–75% yields (88M761; 89MI2). When 7,8,9,10-tetrahydro-1,7-phenanthroline and EMME were reacted in polyphosphate at 160°C for 11 hr, 7-ethyl-7,8,9,10-tetrahydro-



1,7-phenanthroline was isolated in 24% yield in addition to the tetracyclic derivative (**725**, X = N, Y = CH, R = R¹ = H) (88M761).

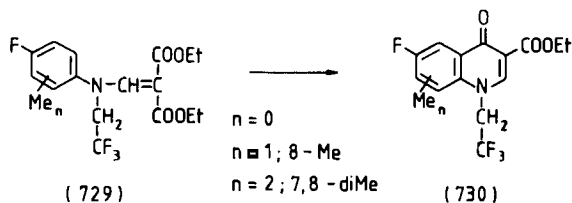
The cyclization of 9-carbazolylmethylenemalonates (**144**, R² = H) in polyphosphoric acid at 140°C for 30 min gave tetracyclic pyrido[3,2,1-*jk*]carbazolecarboxylates (**726**) in good yields [79GEP2914258; 80 JAP(K)145612].

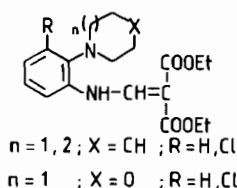
The cyclization of (1,2,3,4-tetrahydroquinolin-1-yl)methylenemalonates (**727**, R² = H, OH; R³ = H) was achieved by heating in polyphosphoric acid at 100–120°C for 0.5–1.0 hr to give benzo[*ij*]quinolizinecarboxylates or carboxylic acids (**728**, R = Et or H), depending on the work-up process (73GEP2264163; 74GEP2415763; 76MIP3, 76USP3969463, 76USP 3985882; 77USP4001243, 77USP4014877). (4-Oxotetrahydroquinolin-1-yl)methylenemalonate (**727**, R¹ = Me; R² = R³ = O; R⁴ = F; R⁵ = R⁶ = H) was cyclized to a tricyclic compound (**728**, R = Et, R¹ = Me, R² = R³ = O, R⁴ = F, R⁵ = R⁶ = H) by treatment in polyphosphoric acid at 150–160°C for 5–10 min (76USP3976651, 76USP3985753). Alkylenedioxy derivatives of **727** (R⁴ = R⁵ = O(CH₂)_nO, n = 1,2) gave 1,3-dioxolo-9,10- and 1,4-dioxino-9,10-benzo[*ij*]quinolizinecarboxylic acid derivatives (**728**, R⁴ = R⁵ = —O(CH₂)_nO—) (77USP4001243, 77USP4014877).



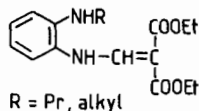
The cyclization of *N*-(2,2,2-trifluoroethyl)-*N*-(4-fluorophenyl)aminomethylenemalonates (**729**) was carried out in polyphosphoric acid at 105–115°C to give quinoline-3-carboxylates (**730**) in moderate yields (79USP4146625).

Aminomethylenemalonates (**731**, **732**, and **733**) could not be cyclized by heating in polyphosphoric acid; only hydrolysis to the parent amines

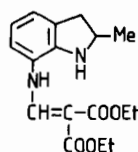




(731)



(732)

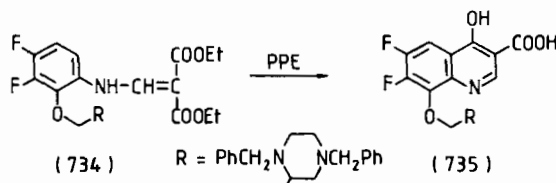


(733)

occurred [75JCS(P1)2409]. Aminomethylenemalonates (**731**) behaved similarly in ethyl polyphosphate.

The ethyl 1-methyl-5,7-dimethoxy-4-oxo-1,4-dihydroquinoline-3-carboxylate was obtained in 55% yield on the cyclization of diethyl *N*-methyl-*N*-(3,5-dimethoxyphenyl)aminomethylenemalonate in polyphosphate at 110°C for 1.5 hr (89JMC807).

The cyclization of *N*-(2-substituted 3,4-difluorophenyl)aminomethylenemalonate (**734**) in polyphosphate at 100°C for 10 hr under nitrogen gave the quinoline-3-carboxylic acid (**735**) after work-up of the reaction mixture (87EUP216345).

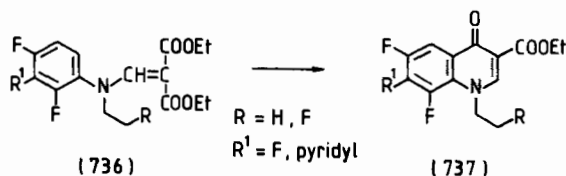


(734)

(735)

N-Substituted *N*-(2,3,4-trifluorophenyl)aminomethylenemalonates (**736**, $R^1 = F$) were cyclized by heating in polyphosphate at 110–115°C for 1 hr to give 1-substituted quinoline-3-carboxylates (**737**, $R^1 = F$) in 48–88% yields [85JAP(K)166681].

The cyclization of *N*-alkyl-*N*-(2,4-difluoro-3-(pyridyl)phenyl)aminomethylenemalonates (**736**, $R^1 = \text{pyridyl}$) was carried out in polyphosphate at 100°C for 30 min [85JAP(K)166678] or at 150°C for 20–30 min (87USP4636506) to give 1-alkylquinoline-3-carboxylates (**737**, $R^1 = \text{pyridyl}$) in 11–65% yields.



(736)

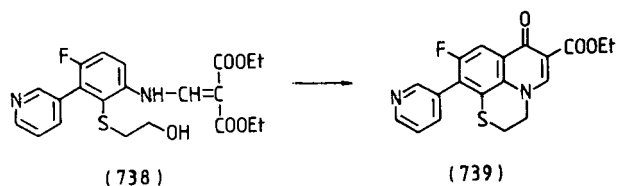
(737)

Diethyl (1,4-benzoxazin-4-yl)methylenemalonates (**136**, R and $R^1 = F$, Cl , $R^2 = H$, Me , CH_2OMe) were cyclized by heating in polyphosphate at 120 – $145^\circ C$ for 1.0 – 2.5 hr to give ethyl pyrido[1,2,3-*de*]-1,4-benzoxazine-6-carboxylates (**718**, R and $R^1 = F$, Cl ; $R^2 = H$, Me , CH_2OMe , $R^3 = Et$) in 64 – 69% yields [82EUP47005, 82JAP(K)203085; 83JAP(K)52290; 84CPB4907, 84EUP101829].

Ethyl 9,10-difluoro-3-methylpyrido[1,2,3-*de*]-1,4-benzoxazine-6-carboxylate (**718**, $R = R^1 = F$, $R^2 = Me$, $R^3 = Et$) was prepared in 75% yield in the one-pot reaction of 7,8-difluoro-3-methyl-3,4-dihydro-2*H*-1,4-benzoxazine and diethyl *N,N*-dimethylaminomethylenemalonate in polyphosphate at 140 – $145^\circ C$ for 1.5 hr [83JAP(K)72588].

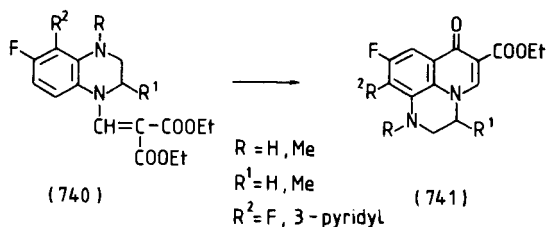
The ring closure of (1,4-benzothiazin-4-yl)-methylenemalonates (**141**, $R = R^3 = H$, $R^1 = F$, 3-pyridyl, $R^2 = F$) in polyphosphate at 130 – $140^\circ C$ for 30 – 60 min gave ethyl pyrido[1,2,3-*de*]-1,4-benzothiazine-6-carboxylates (**719**, $R = R^3 = H$, $R^1 = F$, 3-pyridyl, $R^2 = F$, $R^4 = Et$) in 70 – 79% yields [82JAP(K)203085; 87USP4636506].

The heating of *N*-(2-(2-hydroxyethylthio)-3-(3-pyridyl)-4-fluorophenyl)aminomethylenemalonate (**738**) in polyphosphate at 130 – $145^\circ C$ for 30 min afforded tricyclic pyrido[1,2,3-*de*]-1,4-benzothiazine-6-carboxylate (**739**) (87USP4636506).



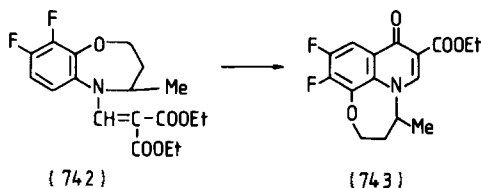
The cyclization of (5,6-difluorotetrahydroquinoxalin-1-yl)methylenemalonates (**740**, $R^2 = F$) by heating in polyphosphate at $140^\circ C$ for 1.0 – 1.5 h gave ethyl pyrido[1,2,3-*d,e*]quinoxaline-6-carboxylates (**741**, $R^2 = F$) in moderate yields [82JAP(K)203085].

The ring closure of diethyl (tetrahydroquinoxalin-1-yl)methylenemalo-



nate (**740**, $R = \text{Me}$, $R^1 = \text{H}$, $R^2 = 3\text{-pyridyl}$) in polyphosphate at $130\text{--}140^\circ\text{C}$ for 30 min afforded pyrido[1,2,3-*de*]quinoxaline-6-carboxylate (**741**, $R = \text{Me}$, $R^1 = \text{H}$, $R^2 = 3\text{-pyridyl}$) in 84% yield (87USP4636506).

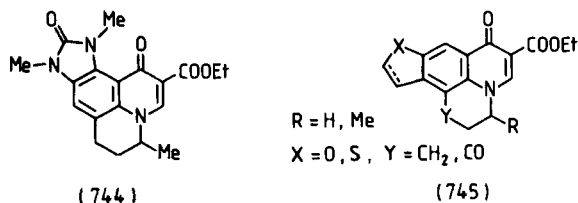
Pyrido[1,2,3-*ef*]-1,5-benzoxazepine-7-carboxylate (**743**) was obtained in moderate yield by the cyclization of (1,5-benzoxazepin-5-yl)methylenemalonate (**742**) on the action of polyphosphate at $150\text{--}160^\circ\text{C}$ for 1 hr [82JAP(K)203085].



The cyclization of (imidazo[4,5-*g*]quinolin-5-yl)methylenemalonate (**146**) by heating in polyphosphate at 130°C afforded benzimidazolo[6,5,4-*ij*]quinolizine carboxylate (**744**) in 50% yield [79JAP(K)154797].

The cyclization of (furo[2,3-*h*]-1,4-benzoxazinyl)methylenemalonate (**156**) by heating in polyphosphate at $130\text{--}140^\circ\text{C}$ for 1 hr afforded furo[2,3-*h*]pyrido[1,2,3-*de*]-1,4-benzoxazine-6-carboxylate (**718**, $R = R^1 = \text{—O—CH—CH}_2\text{—}$, $R^2 = \text{Me}$) in 61% yield (84CPB4923).

The heating of tricyclic methylenemalonates (**150**) in polyphosphate at 120°C gave tetracyclic quinoline-3-carboxylates (**745**, R , X , and Y as in **150**) in 60–79% yields [79JAP(K)163598].

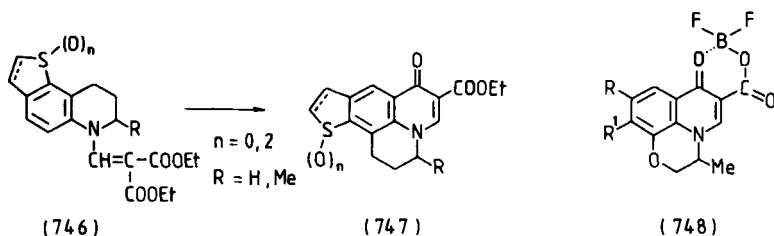


(Thieno[2,3-*f*]quinolin-6-yl)methylenemalonates (**746**) were cyclized by heating in polyphosphate at $110\text{--}130^\circ\text{C}$ for 4–7 hr to give benzo-thieno[5,6,7-*ij*]quinolizine-6-carboxylates (**747**) in 53–68% yields (88AP241).

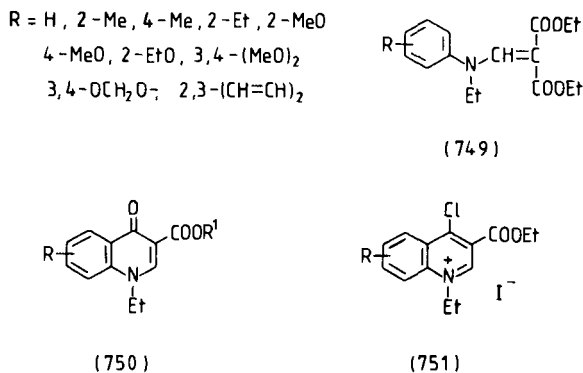
Diethyl (7,8-difluoro-3-methyl-3,4-dihydro-2*H*-benzoxazin-4-yl)methylenemalonate was cyclized in boiling acetic anhydride on the action of boron trifluoride in THF to give a pyrido[1,2,3-*de*]-1,4-benzoxazine-6-

carboxylic acid and boric acid anhydride (**748**, $R = R^1 = F$) in 79–86% yields [85JAP(K)126290].

(1,4-Benzoxazin-4-yl)methylenemalonates (**136**, $R^2 = Me$) were cyclized on the action of boron trifluoride in THF by heating in Dowtherm A at 240–250°C for 30 min to give pyrido[1,2,3-*de*]-1,4-benzoxazines (**748**) in 54–94% yields [83JAP(K)29789].



Nakagome and co-workers effected the successful cyclization of *N*-ethyl-*N*-arylaminomethylenemalonates (**749**) in polyphosphoric acid, prepared from orthophosphoric acid and phosphorus pentoxide; in polyphosphate ester (PPE), prepared from phosphorus pentoxide and anhydrous diethyl ether in chloroform; in phosphoryl chloride; on the action of boron trifluoride etherate; on the action of acetic anhydride and concentrated sulfuric acid; or on the action of phosphorus pentoxide in benzene [71GEP2033971, 71JHC357; 76JAP(K)18440]. Depending on the work-up process, 1-ethyl-4-oxoquinoline-3-carboxylates (**750**, $R^1 = Et$), 1-ethyl-4-oxoquinoline-3-carboxylic acids (**750**, $R^2 = H$) and 3-ethoxycarbonyl-4-chloroquinolinium iodides (**751**) were obtained. Only the cyclization of



N-(3-trifluoromethylphenyl)aminomethylenemalonate (**749**, R = 3-CF₃) proved unsuccessful in boiling phosphoryl chloride. The thermal cyclization of *N*-ethyl-*N*-arylaminomethylenemalonates (**749**) and their ring closure in acetic acid, in acetic anhydride with zinc chloride, or in a melt of aluminium chloride were likewise unsuccessful (71JHC357). The corresponding quinoline was not obtained in a one-pot version when *N*-ethylaniline and EMME were reacted in polyphosphoric acid. Table V shows the yields of quinoline-3-carboxylic acid derivatives obtained from *N*-ethyl-*N*-phenyl- and *N*-ethyl-*N*-(3,4-methylenedioxyphenyl)aminomethylenemalonates (**749**, R = H and 3,4-OCH₂O) under various acidic cyclization conditions.

Diethyl *N*-ethyl-*N*-(3-methyl-5-isoxazolyl)aminomethylenemalonate could not be cyclized under acidic conditions in phosphoryl chloride, polyphosphoric acid or PPE (88JHC231).

Diethyl *N*-ethyl-*N*-(2,5-dibenzoyloxyphenyl)-aminomethylenemalonate was cyclized in hydrofluoric acid at ambient temperature for 3 days to afford ethyl 5,8-dihydroxy-1-ethyl-4-oxo-1,4-dihydroquinoline-3-carboxylate in 62–73% yields (82HCA2645).

TABLE V
CYCLIZATION OF DIETHYL *N*-ETHYL-*N*-PHENYL- AND
N-ETHYL-*N*-(3,4-METHYLENEDIOXYPHENYL)AMINOMETHYLENEMALONATES (**749**) UNDER
ACIDIC CONDITION (71JHC357)

| R 749 | Cyclization agent | Reaction temp(°C) | Conditions period | Product | Yield % |
|-------------------------|--|----------------------|----------------------|----------------------------------|----------------------|
| H | PPA | 110–120 | 15 min | 750 , R ¹ = Et | 76(60 ^a) |
| | PPA | 170–180 | 40 min | 750 , R ¹ = H | 48 |
| | PPE | 100–115 | 3 hr | 750 , R ¹ = Et | 72 |
| | Boron trifluoride | Reflux | 3 hr | 750 , R ¹ = H | 74 |
| | Ac ₂ O-H ₂ SO ₄ | r.t. | 15 min | 750 , R ¹ = H | 54 |
| | P ₂ O ₅ in benzene | Reflux | 4 hr | 750 , R ¹ = Et | 17 ^b |
| | POCl ₃ (+ KI) ^c | Reflux | 3 hr | 751 | 75 |
| 3,4-OCH ₂ O- | PPA | 90–95 | 1 hr | 750 , R ¹ = Et | 79(54 ^a) |
| | PPA | 90–95 | 1 hr | 750 , R ¹ = H | 83 ^d |
| | PPE | 100–110 | 3 hr | 750 , R ¹ = H | 90 |
| | Boron trifluoride | Reflux | 8 hr | 750 , R ¹ = H | 85 |
| | POCl ₃ (+ KI) ^c | 70–80 | 3 hr | 751 | 88 |

^a After recrystallization.

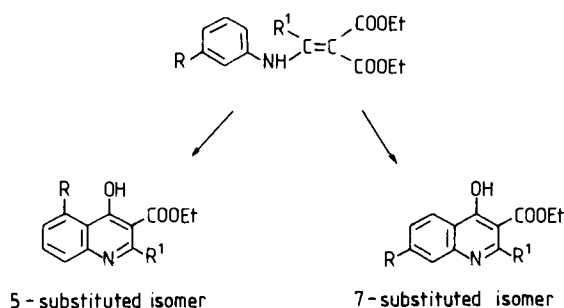
^b 28% of *N*-Ethylaniline was recovered.

^c The quaternary salt (**751**) was prepared as iodide by the use of potassium iodide.

^d The carboxylic acid was isolated after the alkaline treatment of the reaction mixture.

3. CYCLIZATION OF (*m*-SUBSTITUTED PHENYL)AMINOMETHYLENEMALONATES AND RELATED SYSTEMS

If a substituent is present at the meta position of the phenyl ring of phenylaminomethylenemalonate, then the 5- and 7-substituted isomers of quinoline-3-carboxylates may form (see Scheme 43). When the cyclization is carried out thermally, the 7-substituted isomer is usually the major product [e.g., 46JA1204, 46JA1255, 46JA1264, 46JA1268, 46JA1272; 47JA371, 47JA374; 48JA4063; 49BRP627297, 49JA3236, 49JOC277; 50-USP2492801; 52USP2614121; 63BRP942524, 63MI2; 64BEP640906; 65BEP659237; 66BEP670520, 66FRP4148, 66JMC934, 66NEP447, 66-NEP2994; 67USP3316147; 68BRP1120870, 68BRP1122715, 68FRP-1531495, 68SAP5655; 69BRP1168105, 69FRP2001888, 69GEP1814187, 69GEP1908262, 69GEP1908542, 69JMC232, 69SAP5212, 69USP3472859; 70FRP7611, 70FRP7975, 70FRP1581462, 70GEP1912944, 70GEP1936393, 70GEP2021100, 70GEP2033969, 70JMC870, 70JMC1110, 70MIP3; 71-BRP1240446, 71GEP2030899, 71JHC357, 72ACH351, 72ACH469, 72-GEP2220294, 72GEP2224090, 72JMC235, 72MI3; 73AJC907, 73USP-3755332; 74BEP819195, 74FRP2193822, 74GEP2421121, 74GEP2431584, 74JHC849, 74NEP11324; 75BRP1396681, 75GEP2343462, 75JAP(K)-49286, 75JHC557, 75MI1, 75USP3907808; 76H1347, 76MIP1, 76PHA145, 76SZP57834; 77JAP(K)83596, 77JAP(K)125196, 77JMC1001, 77MI4, 77PHA223; 78JMC268, 78JPR937, 78YZ1291; 79CPB1, 79EGP134225, 79EGP136742, 79GEP2840910, 79JHC1353; 80G155, 80GEP2856908, 80JAP(K)33453, 80JMC1358, 80MIP1, 80NEP1752; 81JAP(K)65874; 82CPB3517, 82CPB3530, 82EUP62001, 82EUP67772, 82IJC(B)444, 82JMC57, 82USP4343804; 83ACH241, 83EUP70767; 84EUP106489,



SCHEME 43

84FES95, 84FES910, 84FRP2537140, 84JHC1857; 85BEP902586, 85CPI192554, 85EUP134165, 85EUP153163, 85EUP155244, 85FES237, 85FRP2548664, 85JAP(K)28964, 85MIP1, 85USP4533735; 86EUP172004, 86EUP179239, 86EUP184384, 86FES366, 86FRP2574404, 86JAP(K)37771, 86KFZ313, 86M1339, 86MI13, 86MIP3; 87EUP230053, 87FES3, 87JHC399, 87JHC1509, 87MI6, 87MI7, 87YZ123; 88JPS458, 88USP4777252].

Acidic conditions are more favorable than thermal ring-closure for the formation of 5-substituted isomers. The isomeric ratio of 5- and 7-substituted quinolines is less sensitive to conditions of ring closure in the case of *N*-(3-alkoxy- or 3,4-dialkoxy- or 3,4-alkylenedioxophenyl)aminomethylenemalonates (see Table V and following discussion).

Aqui *et al.* investigated the cyclization of diethyl *N*-(3-substituted phenyl)aminomethylenemalonates (**251**) under different cyclization conditions (75JHC557). For cyclization, they applied a 4 : 7 mixture of concentrated sulfuric acid and acetic anhydride, polyphosphoric acid, polyphosphate (prepared from phosphorus pentoxide and diethyl ether in chloroform), phosphoryl chloride, and Dowtherm A (see Table VI). They found the most effective cyclization conditions were thermal cyclization (heating in Dowtherm A) and polyphosphate.

In the case of phosphoryl chloride, the primary products were 4-chloroquinoline-3-carboxylates. As the quinoline-3-esters were very insoluble, the reaction products were hydrolyzed to quinoline-3-carboxylic acids, and the isomeric ratios were determined by ¹H-NMR in trifluoroacetic acid. Thermal cyclization in Dowtherm A resulted mainly in formation of the 7-substituted isomer. In the case of chloro derivatives (**250**), only traces of 5-isomer could be detected. [Earlier, others observed and reported the formation of a small amount of the 5-isomer too (e.g., 46JA1204; 47JA374).

Under acidic conditions, the formation of a nearly 1 : 1 mixture of 5- and 7-substituted quinoline-3-carboxylates, with a slight excess of the former, was observed from the 3-chloro- and 3-methyl derivatives. The cyclizations of 3-nitro, 3-trifluoromethyl, and methoxy derivatives were carried out only in polyphosphate to give mainly the 7-substituted isomers.

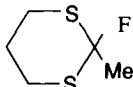
When the qualitative data of the various authors are compared, it seems that the cyclization of *N*-(3-alkoxyphenyl)aminomethylenemalonates is not too sensitive to the cyclization conditions, and mainly 7-alkoxyquinoline-3-carboxylates are obtained.

The yield of the cyclization of *N*-(3-nitrophenyl)aminomethylenemalonate (**752**, R = H) in polyphosphate did not improve significantly when the *N*-ethyl derivative (**752**, R = Et) was applied, but the isomeric ratio was shifted towards the 5-substituted compound (**754**) (75JHC557).

Smrz *et al.* investigated the ring closure of diethyl *N*-ethyl-*N*-(3,4-methylenedioxophenyl)aminomethylenemalonate (**286**) under acidic conditions

TABLE VI

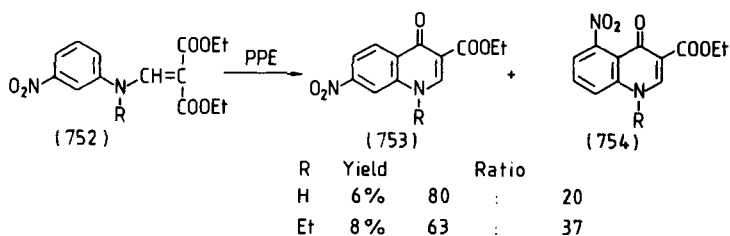
RATIO OF 7- AND 5-SUBSTITUTED 4-HYDROXYQUINOLINE-3-CARBOXYLATES (**759** AND **758**) FORMED BY THE CYCLIZATION OF DIETHYL *N*-(3-SUBSTITUTED PHENYL)AMINOMETHYLENEMALONATES (**757**)

| R | R ¹ | % Yield ^a | | | | | | References |
|---|----------------|------------------------------|--|---------------|---------------|-------------------|-------------------------------|-------------------|
| | | Dowtherm A | Ac ₂ O-H ₂ SO ₄ | PPE | PPA | POCl ₃ | P ₂ O ₅ | |
| OMe | H | | | 46 (100:0) | | | | 75JHC557 76MI5 |
| CF ₃ | H | | | 30 (91:9) | | | | 75JHC557 76MI4 |
| NO ₂ | H | 85 ^b ? (100:0) | | 6 (80:20) | | | | 75JHC557 76MI4 |
| Me | H | 82 (90:10) | 20 (40:60) 32 (37:63) | 76 (43:57) | 15 (35:65) | 67 (42:58) | | 75JHC557 76MI3 |
| Cl | H | 68 (100:?) | 21 (48:52) | 73 (45:55) | 14 (46:54) | 26 (48:52) | | 75JHC557 |
| Cl | F | 70 ^c (100:?) | 10.3 (45:55) | 55 (52:48) | 21 (48:52) | 17.6 (25:75) | 11 (63:27) | 86MI13 (87MI7) |
| NO ₂ | Cl | 80.9 (50:50) | | | | | | 79CPB1 |
| AcOCH ₂ | H | 64.4 (4:1) | | | | | | 82CPB3517 |
| AcOCH ₂ | F | 89 (100:?) | | | | | | 82CPB3530 |
| Me | F | 83 (4:1) | | | | | | 82CPB3530 |
| Ac | H | (1:4) | | | | | | 87JHC1509 |
| Ac | F | 62.6 (1:4) | | | | | | 87JHC1509 |
|  | F | 68 (100:0) | | | | | | 87JHC1509 |

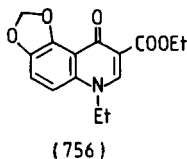
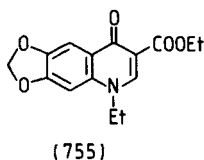
^a Ratio enclosed in parentheses.

^b 47JA374.

^c 87EUP230053.

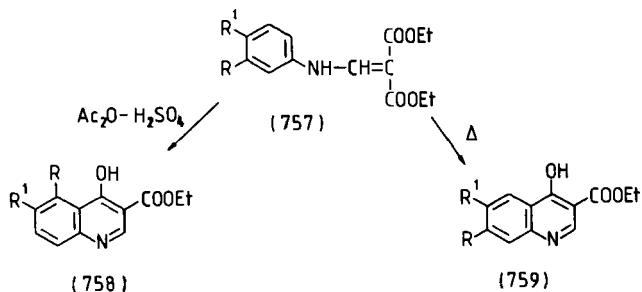


(borontrifluoride etherate, phosphoric acid, phosphoryl chloride, and a mixture of acetic anhydride and concentrated sulfuric acid). In addition to the linear isomer (**755**), the angular one (**756**) was formed in only 1,5% yields, depending on the cyclization conditions. The lowest yield of angular isomer (**756**) (1–2%) was achieved on the action of borontrifluoride



etherate, while the highest yield was obtained in a mixture of acetic anhydride and concentrated sulfuric acid (83MI3). The isomeric tricyclic compounds (**755** and **756**) were separated by fractional crystallization from 20% hydrochloric acid.

Mapara and Desai carried out the cyclization of *N*-(3-substituted phenyl)aminomethylenemalonates (**757**, $R^1 = H$) in a 2 : 1 mixture of acetic anhydride and concentrated sulfuric acid and in diphenyl ether (54JIC951). Acidic conditions yielded mainly 5-substituted quinoline-3-carboxylates (**758**, $R^1 = H$), whereas on heating in diphenyl ether, the 7-substituted compounds (**759**, $R^1 = H$) were the major products.



Renault *et al.* cyclized *N*-(3-methylphenyl)aminomethylenemalonate (**757**, $R = \text{Me}$, $R^1 = H$) in a mixture of acetic anhydride and concentrated sulfuric acid to give a mixture of 5- and 7-methyl-quinoline-3-carboxylates (**758** and **759**, $R = \text{Me}$, $R^1 = H$) (76MI3). The ratio of the 5- and 7-methyl isomers was determined by $^1\text{H-NMR}$ (see Table VI). Mapara and Desai reported that only the 5-methyl isomer (**758**, $R = \text{Me}$, $R^1 = H$) was obtained, in 74% yield, under similar conditions (54JIC951).

In the thermal cyclization of *N*-(3-nitro-, 3-trifluoromethyl-, and 3-methoxyphenyl)aminomethylenemalonates (**757**, $R = \text{NO}_2$, CF_3 , OMe , $R^1 = H$), only the presence of 7-substituted quinolines (**759**, $R = \text{NO}_2$, CF_3 , OMe , $R^2 = H$) could be detected by $^1\text{H-NMR}$ (76MI4, 76MI5).

Later, starting from *N*-(3-nitrophenyl)aminomethylenemalonate (**752**, $R = H$), Cidra and Sleiter prepared 5- and 7-nitro-4-chloroquinolines in 1 : 2 ratio in several steps. In the first step of the thermal ring closure in

diphenyl ether, a mixture of 5- and 7-nitroquinoline-3-carboxylates (**754** and **753**, R = H) was obtained (80G155).

The thermal cyclization of *N*-(3-acetoxymethyl)phenyl aminomethylenemalonate (**757**, R = CH₂Ac, R¹ = H) by heating in diphenyl ether at 250–255°C for 15 min gave a 1 : 4 mixture of 5- and 7-(acetoxymethyl)quinoline-3-carboxylates (**758** and **759**, R = CH₂OAc, R¹ = H) in 64% yield. The major isomer (**759**, R = CH₂OAc, R¹ = H) was isolated by crystallization from DMF (82CPB3517).

Shah and Coats prepared a series of 7-substituted quinoline-3-carboxylates (**759**, R¹ = H) in 63–98% yields by thermal cyclization of diethyl *N*-(3-substituted phenyl)aminomethylenemalonates (**757**, R¹ = H) in diphenyl ether at 250–260°C (77JMC1001). *N*-(3-Cyanophenyl)aminomethylenemalonate (**757**, R = CN, R¹ = H) gave 7-cyanoquinoline-3-carboxylate (**759**, R = CN, R¹ = H) (76PHA145; 77JMC1001) and not the 5-cyano isomer (**758**, R = CN, R¹ = H) as stated earlier (47JA374). The thermal cyclization of (3-sulfonamidophenyl)aminomethylenemalonate (**757**, R = H₂NSO₂, R¹ = H) was unsuccessful (77JMC1001).

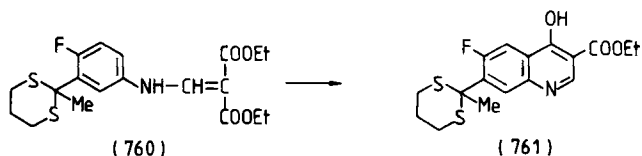
Lee *et al.* reported that the thermal ring closure of diethyl *N*-(3-cyano-4-fluorophenyl)aminomethylenemalonate (**757**, R = CN, R¹ = F) in Dowtherm A led to the formation of 5-cyano-6-fluoro-4-hydroxyquinoline-3-carboxylate (**759**, R = CN, R¹ = F) in very good yield (89MI1).

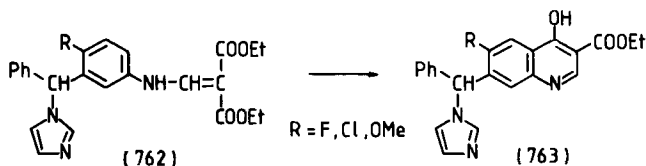
N-(3-Hydroxyphenyl)aminomethylenemalonate (**757**, R = OH, R¹ = H) was cyclized on the action of polyphosphoric acid in phosphoryl chloride at 100°C for 2 hr to give 4,5-dihydroxyquinoline-3-carboxylate (**758**, R = OH, R¹ = H) in 67% yield [81JAP(K)65874].

The thermal cyclization of *N*-(3-acetyl- and 3-acetyl-4-fluorophenyl)aminomethylenemalonates (**757**, R = Ac, R¹ = H, F) in boiling Dowtherm A gave a 4 : 1 mixture of the isomeric 5- and 7-acetylquinoline carboxylates (**758** and **759**), R = Ac, R¹ = F) (87JHC1509).

If *N*-[3-(2-methyl-1,3-dithian-3-yl)phenyl]aminomethylenemalonate (**760**) was used instead of the acetyl derivative (**757**, R = Ac, R¹ = F), only the 7-substituted quinoline-3-carboxylate (**761**) was obtained in 68% yield (85EUP153163; 87JHC1509).

The ring closure of arylaminomethylenemalonates (**762**) in a 1 : 3 mixture of polyphosphoric acid and phosphoryl chloride at 70°C for 4 hr afforded quinoline-3-carboxylates (**763**) in 56–78% yields (87JHC399).

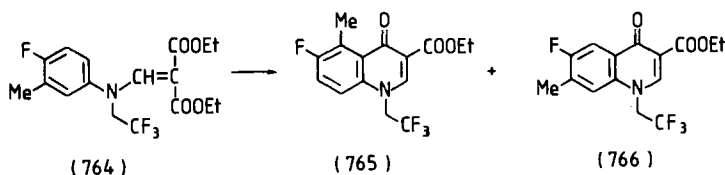




Approximately a 1 : 1 mixture of isomeric 5- and 7-nitro-6-chloroquinoline-3-carboxylates (**758** and **759**, $\text{R} = \text{NO}_2$, $\text{R}^1 = \text{Cl}$) was obtained in 81% yield on the thermal cyclization of *N*-(3-nitro-4-chlorophenyl)aminomethylenemalonate (**757**, $\text{R} = \text{NO}_2$, $\text{R}^1 = \text{Cl}$) in boiling Dowtherm A for 30 min (79CPB1).

A 1 : 4 mixture of isomeric quinoline-3-carboxylates (**758** and **759**, $\text{R} = \text{Me}$, $\text{R}^1 = \text{F}$) was obtained in 83% yield on the thermal cyclization of *N*-(3-methyl-4-fluorophenyl)aminomethylenemalonate (**757**, $\text{R} = \text{Me}$, $\text{R}^1 = \text{F}$) in diphenyl ether at 250–255°C for 15 min (82CPB3530).

The cyclization of *N*-(2,2,2-trifluoroethyl)-*N*-(3-methyl-4-fluorophenyl)aminomethylenemalonate (**764**) by heating in polyphosphoric acid at 105–115°C afforded a mixture of the 5- and 7-methyl isomers (**765** and **766**) (79USP4146625).

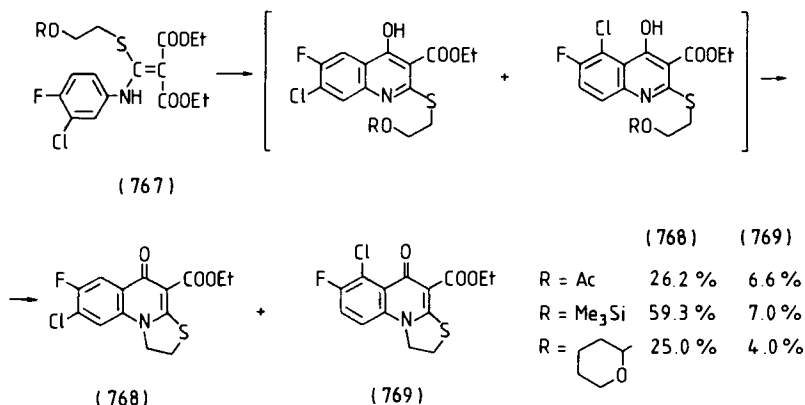


Guo *et al.* investigated the ring closure of *N*-(4-fluoro-3-chlorophenyl)aminomethylenemalonate (**757**, $\text{R} = \text{Cl}$, $\text{R}^1 = \text{F}$) under acidic conditions (see Table VI). A mixture of 5- and 7-chloro-6-fluoroquinoline-3-carboxylates (**758** and **759**, $\text{R} = \text{Cl}$, $\text{R}^1 = \text{F}$) was obtained, in 10–55% yields. The best yield was achieved in polyphosphate (86MI113; 87MI17).

N-(4-Fluoro-3-chlorophenyl)aminomethylenemalonate (**757**, $\text{R} = \text{Cl}$, $\text{R}^1 = \text{F}$) was cyclized in the melt by heating at 250–265°C for 30 min to give 6-fluoro-7-chloroquinoline-3-carboxylate (**759**, $\text{R} = \text{Cl}$, $\text{R}^1 = \text{F}$) in 70% yield (87EUP230053).

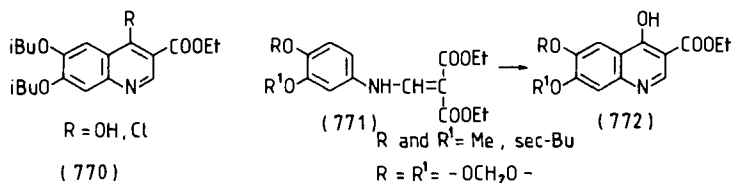
Isomeric 6- and 8-chloro-7-fluorothiazolo[3,2-*a*]quinolines (**768** and **769**) were prepared in 29–66% yields by the thermal cyclization of [(2-substituted ethyl)thio][(3-chloro-4-fluorophenyl)amino]methylenemalonates (**767**) in diphenyl ether at 250°C for 5 min (82EUP58392).

Harris studied the cyclization of *N*-(3,4-diisobutoxyphenyl)aminometh-



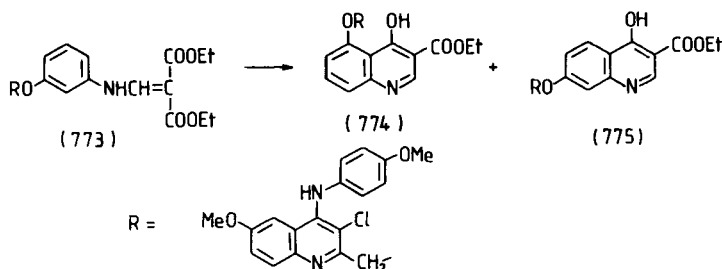
ylenemalonate (**257**, R = *i*Bu) under acidic conditions (71S256; 72S625). 4-Hydroxyquinoline-3-carboxylate (**770**, R = OH) was obtained in 78% yield in polyphosphoric acid at 168–175°C for 1 hr, in 91% yield in polyphosphate (prepared from phosphorus pentoxide and ethanol in xylene) at 138–141°C for 30 min, and in 90% yield by the action of a mixture of phosphoryl chloride and polyphosphoric acid in boiling toluene for 20 min. 4-Chloroquinoline-3-carboxylate (**770**, R = Cl) was prepared in 55% yield in phosphoryl chloride at 100°C for 2 hr.

N-(3,4-Disubstituted phenyl)aminomethylenemalonates (**771**) were cyclized by heating in polyphosphate at 100–120°C for 2 hr to give quinoline-3-carboxylates (**772**) in 42–72% yields (83ACH241).



The cyclization of *N*-(3-substituted phenyl)aminomethylenemalonate (**773**) in boiling diphenyl ether for 5 min gave a mixture of isomeric 5- and 7-substituted quinoline-3-carboxylate (**774** and **775**) in moderate yield [82IJC(B)444]. The 7-substituted isomer (**775**) was the major product.

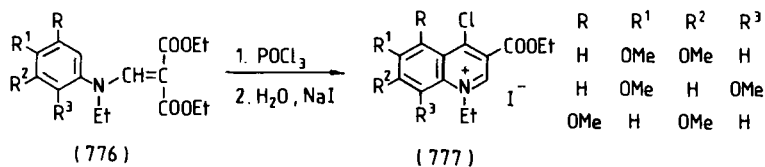
The thermal ring closure of diethyl *N*-(3-aminophenyl)aminomethylenemalonate (**757** R = NH₂, R' = H) and its 4-fluoro derivative (**757**, R = NH₂, R' = F) in boiling diphenyl ether in the presence of acetic anhydride gave the corresponding ethyl 7-acetamido-4-hydroxyquinoline-



3-carboxylate (**759**, R = NHAc, R¹ = H, F) in 45% and 63% yields, respectively (85EUP134165, 85FRP2548664).

Decoquat was prepared in 73% yield from diethyl *N*-(3-ethoxy-4-*n*-decyloxyphenyl)aminomethylenemalonate (**771**, R = decyl, R¹ = Et) in boiling xylene on the action of phosphorus pentoxide for 2 hr (76MIP1).

1-Ethyl-4-chloroquinolinium iodide (**777**) was obtained by the treatment of *N*-(dimethoxyphenyl)aminomethylenemalonates (**776**) in boiling phosphoryl chloride for 4 hr. The excess of phosphoryl chloride was then evaporated off under reduced pressure; the residue was dissolved in water, and excess sodium iodide was added to the aqueous filtrate to give the crystalline iodide (**777**) (79JHC1353).

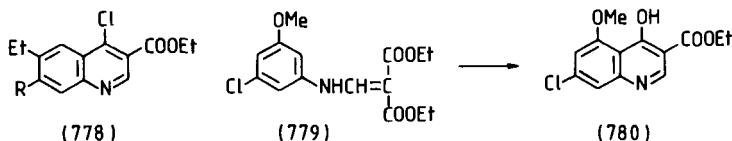


The cyclization of *N*-(3-substituted 4-ethylphenyl)aminomethylenemalonates (**757**, R = 4-BrPhOCH₂, octadecyloxy, R¹ = Et) in phosphoryl chloride at 100–130°C for 4 hr afforded 7-substituted 6-ethyl-4-chloroquinoline-3-carboxylates (**778**, R = 4-BrPhOCH₂, octadecyloxy) in 94–98% yields (79EGP134225, 79EGP136742).

The ring closure of *N*-[4-ethyl-3-(2-chlorophenoxy)methylphenyl]aminomethylenemalonate (**757**, R = 2-ClPhOCH₂, R¹ = Et) in polyphosphate (prepared from phosphorus pentoxide and ethanol in xylene at 100°C) at 150°C for 30 min afforded quinoline-3-carboxylate (**759**, R = 2-ClPhOCH₂, R¹ = Et) in 74% yield (79EGP136742).

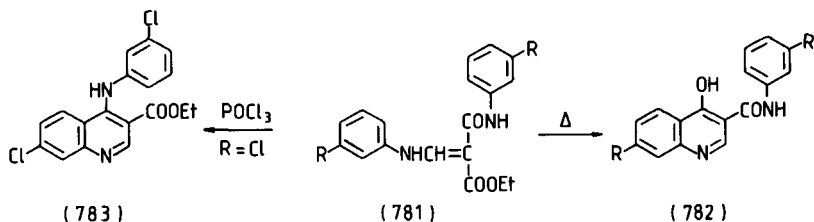
A mixture of 3-(trifluoromethoxy)aniline and EMME was heated in diphenyl ether at 110°C for 1 hr, and then at 240°C for 3 hr, to give 7-(trifluoromethoxy)quinoline-3-carboxylate (**759**, R = CF₃O, R¹ = H) in 90% yield (74FRP2193822).

The thermal cyclization of *N*-(3-chloro-5-methoxyphenyl)aminomethylenemalonate (**779**) in boiling diphenyl ether for 20 min gave 7-chloro-5-methoxyquinoline-3-carboxylate (**780**) (47JA371).



7-Chloro-4-hydroxyquinoline was prepared in 91–93% yields in a one-step procedure, when *N*-(3-chlorophenyl)aminomethylenemalonate (**250**) was heated in boiling Dowtherm A for 0.5–2 hr, and the reaction mixture was then treated with water at the same temperature for 1–2 hr (73MIP2).

The thermal ring closure of *N*-(3-chlorophenyl)aminomethylenemalonate (**781**, R = Cl) to quinoline-3-carboxamide (**782**, R = Cl) in 50–59% yields was carried out in boiling diphenyl ether (46JA1251, 46JA1253) in a higher dilution than for its diester derivative (**250**) (46JA1204). A similar reaction took place with phenylaminomethylenemalonate (**781**, R = H) (50JCS607).



The ring closure of *N*-(3-chlorophenyl)aminomethylenemalonate (**781**, R = Cl) and the 4-chloro derivative in boiling benzene on the action of phosphoryl chloride for 6–10 hr afforded the corresponding 4-(arylamino)quinoline-3-carboxylate (e.g., **783**) in 57–65% yield (46JA1246). If the cyclization of **781** (R = Cl) was carried out in boiling xylene by the action of phosphorus pentoxide, compound **783** was obtained in only 21% yield.

Ujhidy and co-workers studied the thermal ring closure of *N*-(3-chlorophenyl)aminomethylenemalonate (**250**) to 7-chloro-4-hydroxyquinoline-3-carboxylate (**759**, R = Cl, R¹ = H) in Dowtherm A containing 5% or 10% of paraffin oil at 230°C, 235°C, 240°C, 245°C, 250°C, and 255°C in different reactors (a continuous tank reactor, a batch tank reactor, a cascade of

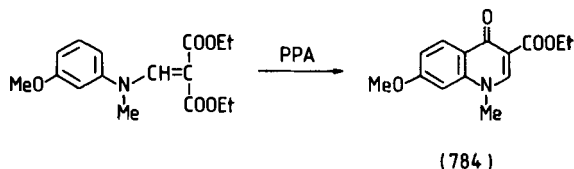
three members, a traditional rotary film apparatus, and a climbing film apparatus) (75ACH279, 75MI1; 77MI2; 78MI4). They determined the reaction constants. The highest yield and the purest product were attained in the batch tank reactor.

The ring closure of *N*-(4-butyryl-3-methylphenyl)aminomethylenemalonate (**757**, $R = \text{Me}$, $R^1 = \text{PrCO}$) on heating in boiling diphenyl ether gave 6-butyryl-7-methylquinoline-3-carboxylate (**759**, $R = \text{Me}$, $R^1 = \text{PrCO}$) (85CPI192554).

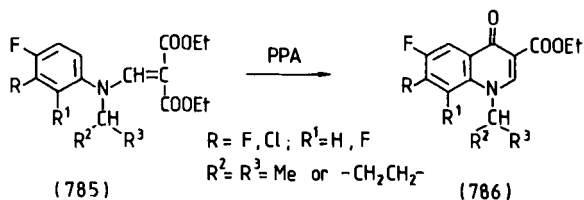
The thermal cyclization of 4-fluoro-3-(1-pyrrolyl)phenylaminomethylenemalonate (**757**, $R = 1\text{-pyrrolyl}$, $R^1 = \text{F}$) in diphenyl ether at 250°C for 5 min gave 6-fluoro-7-(1-pyrrolyl)quinoline-3-carboxylate (**759**, $R = 1\text{-pyrrolyl}$, $R^1 = \text{F}$) in 55% yield (86FRP2574404).

N-Methyl-*N*-(3-methoxyphenyl)aminomethylenemalonate was cyclized by heating in polyphosphoric acid at 100°C for 40 min to give 1-methyl-7-methoxyquinoline-3-carboxylate (**784**) (86EUP172004).

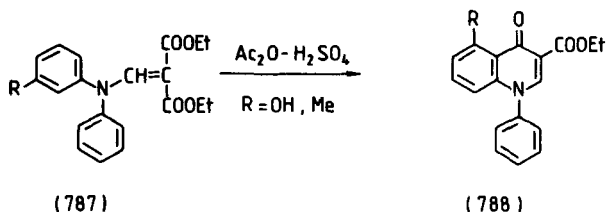
Rosoxacin was prepared in 47% yield by the cyclization of diethyl *N*-ethyl-*N*-[3-(4-pyridyl)phenyl]aminomethylenemalonate in polyphosphoric acid at 165°C for 1 hr, followed by hydrolysis of the corresponding quinoline-3-carboxylate (85USP4533735).



The ring closure of *N*-isopropyl- or *N*-cyclopropyl-*N*-(substituted phenyl)aminomethylenemalonates (**785**) in polyphosphoric acid at 100–110°C for 1 hr gave quinoline-3-carboxylates (**786**) in good yields (85JAP(K)28964, 85JAP(K)126271).

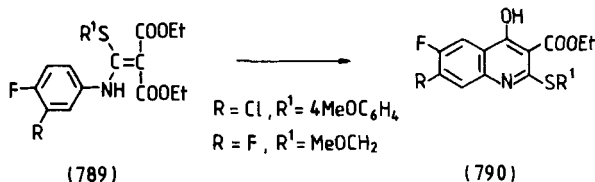


On the cyclization of *N*-(3-substituted phenyl)-*N*-phenylaminomethylenemalonates (**787**) in a 2 : 1 mixture of acetic acid and concentrated sulfuric acid, 5-substituted 1-phenylquinoline-3-carboxylates (**788**) were isolated (69BRP1147336).

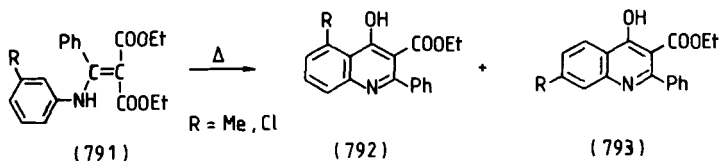


The thermal cyclization of [(3-chloro-4-fluorophenyl)amino][4-methoxyphenyl]methylthio]methylenemalonate (**789**, $R = \text{Cl}$, $R^1 = 4\text{-MeOC}_6\text{H}_4$) in diphenyl ether at 250°C for 3 min gave 2-substituted quinoline-3-carboxylate (**790**, $R = \text{Cl}$, $R^1 = 4\text{-MeOC}_6\text{H}_4$) in 66% yield (82EUP58392).

The thermal cyclization of (methoxymethylthio)(3,4-difluorophenyl-amino)methylenemalonate (**789**, $R = \text{F}$, $R^1 = \text{MeOCH}_2$) by heating in diphenyl ether at 240°C for 5–10 min yielded 6,7-difluoro-2-(methoxymethylthio)quinoline-3-carboxylate (**790**, $R = \text{F}$, $R^1 = \text{MeOCH}_2$) (87BRP2190376).

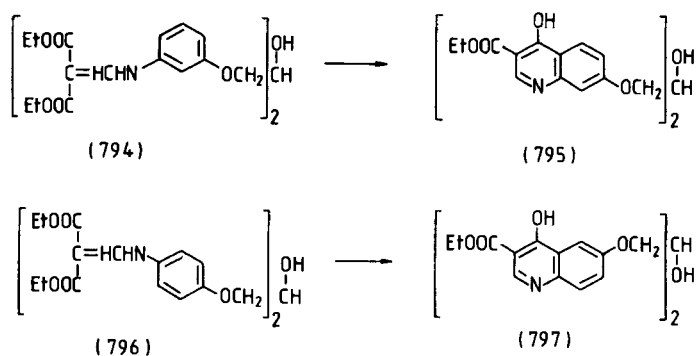


Shah and Heeramanek obtained isomeric mixtures of 5- and 7-substituted 2-phenylquinoline-3-carboxylates (**792** and **793**) on the cyclization of phenyl-[(3-substituted phenyl)amino]methylenemalonates (**791**) in the melt at above 180°C (36JCS428). In the case of the methyl derivative (**791**, $R = \text{Me}$), two isomers (**792** and **793**, $R = \text{Me}$) were separated by crystallization five times from ethyl acetate.

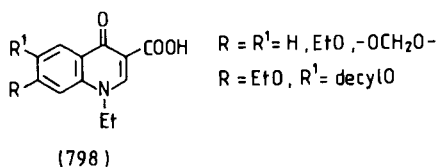


The thermal cyclization of bis(aminomethylenemalonates) (**794** and **796**) in boiling Dowtherm A for 30 min afforded bis(quinoline-3-carboxylates) (**795** and **797**) in moderate yields (80GEP2586908).

The reaction of phenylaminomethylenemalonates (**757**) in triethyl phos-



phate at 220–225°C for 1 hr, followed by alkaline hydrolysis, gave 1-ethyl-4-oxo-1,4-dihydroquinoline-3-carboxylic acids (**798**) in good yields. The ring closure was accompanied by *N*-ethylation (70MIP1; 77TL4545).

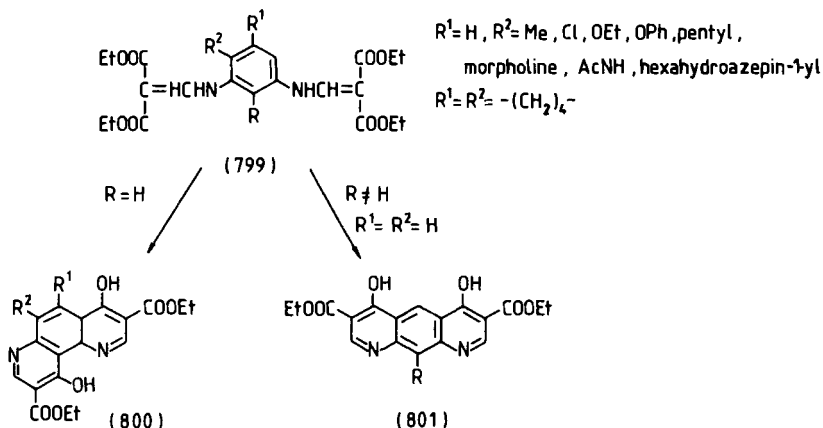


Bis(aminomethylenemalonate) (**799**, $\text{R} = \text{R}^1 = \text{H}$, $\text{R}^2 = \text{Me}$) was added to preheated paraffin oil at 245–260°C, and the reaction mixture was stirred at 250–255°C for 20 min to give 1,7-phenanthroline (**800**, $\text{R} = \text{R}^1 = \text{H}$, $\text{R}^2 = \text{Me}$) in 81% yield (83JHC681).

1,7-Phenanthroline-3,9-dicarboxylates (**800**, $\text{R} = \text{R}^1 = \text{H}$, $\text{R}^2 = \text{H}$, Cl) were also obtained in good yields from bis(aminomethylenemalonates) **799**, $\text{R} = \text{R}^1 = \text{H}$, $\text{R}^2 = \text{H}$, Cl) by heating in boiling Dowtherm A, diphenyl ether (54JA1109; 84MI4), or mineral oil at 270–275°C (54JA1109).

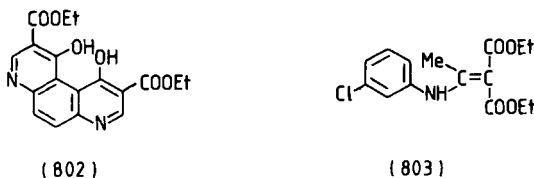
The thermal cyclization of *m*-phenylenediamine derivatives (**799**) by heating in diphenyl ether afforded angular 1,7-phenanthroline-3,9-dicarboxylate (**800**), if a substituent was not present at position 2 of the phenyl ring of **799** ($\text{R} = \text{H}$), but the linear pyrido[3,2-*g*]quinolinecarboxylate (**801**, $\text{R} = \text{Me}$, $\text{R}^1 = \text{R}^2 = \text{H}$) was prepared from the 2-methyl-substituted derivative (**799**, $\text{R} = \text{Me}$, $\text{R}^1 = \text{R}^2 = \text{H}$) (72GEP2220294).

Whereas the cyclization of bis(aminomethylenemalonate) (**168**, $\text{R} = \text{H}$) by heating in paraffin oil at 255°C was not successful, the cyclization did occur in boiling diphenyl ether to give the angular 4,7-phenanthroline-2,9-dicarboxylate (**802**) in 88% yield (49JCS1017). When the condensation and ring closure were carried out in a one-pot procedure, starting from *p*-



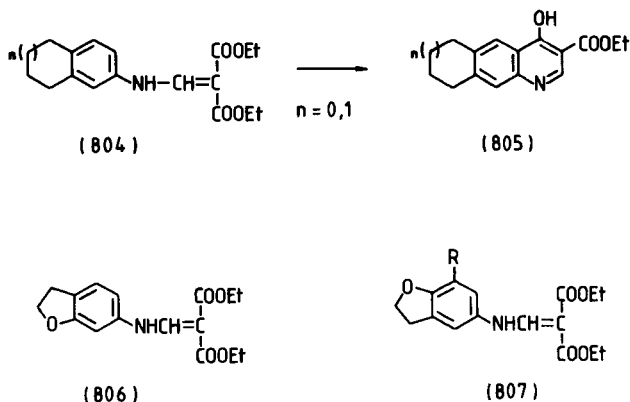
phenylenediamine and EMME in diphenyl ether, the angularly fused tricycle (**802**) was prepared in 80% yield.

3-Chloroaniline was reacted with diethyl acetylmalonate at room temperature in vacuo over anhydrous CaCl_2 for 10 days. The resulting crotonate (**803**) was cyclized in boiling diphenyl ether for 40 min to give 7-chloro-4-hydroxy-2-methylquinoline-3-carboxylate in 17% yield (73USP3755332).



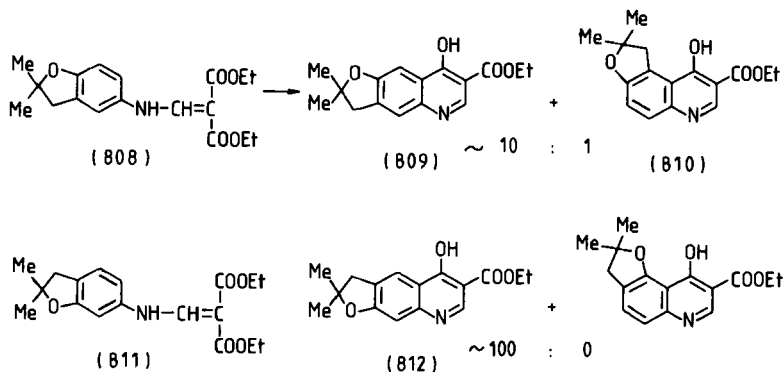
The ring closure of *N*-(3,4-polymethylenephenyl)aminomethylenemalonates (**804**) by heating in a high-boiling solvent gave linearly annelated cycloalkano[*g*]quinoline-3-carboxylates (**805**) (69SAP5212; 70GEP1912944).

Derivatives of *N*-(2,3-dihydrobenzofuran-6-yl)aminomethylenemalonate (**806**) can be regarded as *N*-(3-alkoxyphenyl)aminomethylenemalonate derivatives, and those of *N*-(2,3-dihydrobenzofuran-5-yl)aminomethylenemalonate (**807**, $R = \text{H}$) can be regarded as *N*-(3-alkylphenyl)aminomethylenemalonates. Since the ratio of angular (5-substituted) and linear (7-substituted) products is more sensitive to the circumstances of cyclization in the case of *N*-(3-alkylphenyl)aminomethylenemalonate (i.e., **807**, $R = \text{H}$) than for *N*-(3-alkoxyphenyl)aminomethy-



lenemalonate (i.e., **806**, $R = H$) (see Table V), we may expect that a higher amount of angular tricyclic quinolines will be formed in the cyclization of compound **807** than in the case of compound **806**.

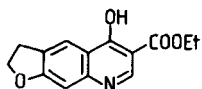
Cruickshank *et al.* reported that the thermal cyclization of 5-benzofuran-ylaminomethylenemalonate (**808**) in boiling diphenyl ether for 30 min gave a 10 : 1 mixture of the linearly and angularly fused tricycles (**809** and **810**) in 75% yield, while in the case of 6-benzofuranylaminomethylenemalonate (**811**), only formation of the linear product (**812**) could be detected (70JMC1110).



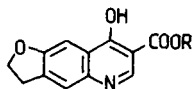
On the thermal cyclization of compound (**806**) in boiling Dowtherm A for 30 min, only the linear product (**813**) was obtained in 59% and 67% yields (75GEP2416519; 77MI4). In these cases, however, the product was not investigated by the use of thin-layer chromatography (TLC) or NMR.

Albrecht reported that the thermal ring closure of the isomeric 5-benzofuranylaminomethylenemalonate (**807**, $R = H$) in boiling Dowtherm A for

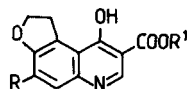
20 min afforded a 4:1 mixture of the linear and angular products (**814**, $R = Et$ and **815**, $R = H$, $R^1 = Et$) in 49% yield (72LA55). If an additional methoxy group was present at position 7 of compound **807** ($R = OMe$), then the influence of the methoxy group was stronger, and furo[3,2-*f*]quinoline-8-carboxylate (**815**, $R = OMe$, $R^1 = Et$) was the only product, in 86% yield.



(813)

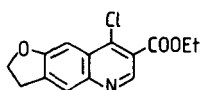


(814)

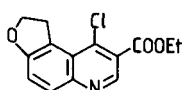


(815)

When the cyclization of compound **807** ($R = H$) was carried out in boiling phosphoryl chloride, the isomeric chloro derivatives (**816** and **817**) were obtained in 98% yield. They were separated by the use of column chromatography, in which the linear product (**816**) was prepared in 50% yield, and the angular product (**817**) was prepared in 27% yield (74GEP2335760). Earlier, 31% of furo[2,3-*g*]quinolinecarboxylic acid (**814**, $R = H$) and 7% of furo[3,2-*f*]quinolinecarboxylic acid (**815**, $R = R^1 = H$) were isolated from the cyclization of compound **807** ($R = H$) in phosphoryl chloride and after hydrolysis of the reaction product with hydrochloric acid (71GEP2030899).

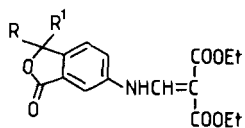


(816)

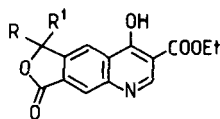


(817)

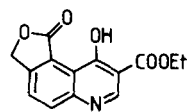
On the thermal cyclization of benzofuranylaminomethylenemalonate (**818**, $R = R^1 = H$) in boiling Dowtherm A for 20 min, the isomeric furo[3,4-*g*]- and furo[3,4-*f*]quinolinecarboxylates (**819**, $R = R^1 = H$, and **820**) were isolated in 49% and 15% yields, respectively (71GEP2030899). Under similar conditions, the dioxo derivative (**818**, $R = R^1 = O$) afforded only the linear product (**819**, $R = R^1 = O$) in 52% yield (71GEP2030899).



(818)

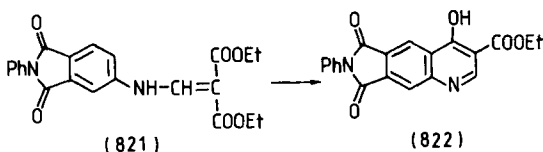


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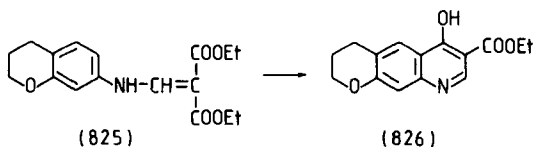
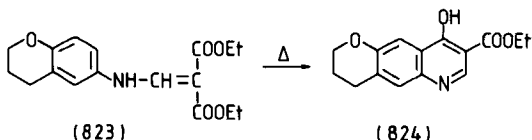


(820)

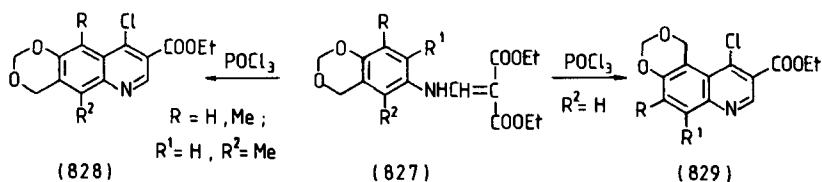
The thermal cyclization of *N*-(1,3-dioxoisindol-5-yl)aminomethylenemalonate (**821**) in boiling Dowtherm A gave pyrrolo[3,4-*g*]quinoline-3-carboxylate (**822**) (87MI1).



The thermal ring closure of 6- and 7-chromanylaminomethylenemalonates (**823** and **825**) in Dowtherm A at 240°C for 15 min gave only linear products (**824** and **826**) in 78% and 70% yields, respectively (70GEP1936393; 72BRP1283900).

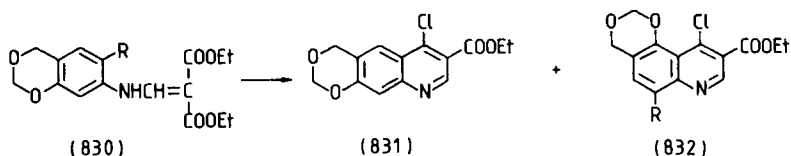


The cyclization of *N*-(1,3-benzodioxan-6-yl)aminomethylenemalonates (**827**, $R^2 = H$) in boiling phosphoryl chloride for 6–18 hr afforded angular 7-chloro-1,3-dioxino[5,4-*f*]quinoline-9-carboxylates (**829**) in 25–85% yields (72GEP2139212, 72MI4). Earlier, the reaction product of compound **827** ($R = R^1 = R^2 = H$) was incorrectly given as the linearly anelated tricycle **828** ($R = R^2 = H$) (70GEP1936393; 72BRP1283900). 9-Chloro-1,3-dioxino[4,5-*g*]quinoline-8-carboxylates (**828**, $R^2 = Me$) were obtained un-



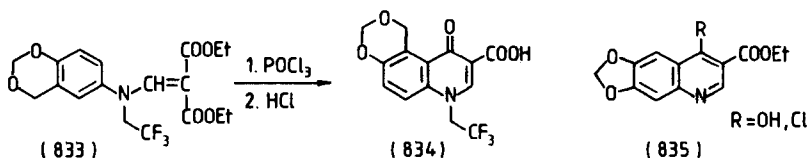
der similar conditions, only if $R^2 \neq H$, in 50–62% yields [72CR(D)1583, 72GEP2139212, 72MI5].

At the same time, the ring closure of *N*-(1,3-benzodioxan-7-yl)aminomethylenemalonate (**830**, $R = H$) in boiling phosphoryl chloride for 12 hr gave a mixture of 1,3-dioxino[4,5-*g*]quinoline (**831**) and 1,3-dioxino[4,5-*f*]quinoline (**832**, $R = H$), with an excess of the linear product (**831**) (72MI5). Starting from the methyl derivative of compound **830** ($R = Me$), the angular product (**832**, $R = Me$) was prepared in 40% yield (72MI4).



7-(2,2,2-Trifluoroethyl)-1,3-dioxino[5,4-*f*]quinoline-9-carboxylic acid (**834**) was obtained by the cyclization of *N*-(2,2,2-trifluoroethyl)-*N*-(1,3-benzodioxan-6-yl)aminomethylenemalonate (**833**) in boiling phosphoryl chloride [77JAP(K)142098].

N-(3,4-Methylenedioxyphenyl)aminomethylenemalonate (**258**) was cyclized by heating in Dowtherm A at 254–257°C [76JAP(K)86497] or in polyphosphate at 110–120°C for 1 hr [72JCS(P1)173] to give 1,3-dioxino[*g*]quinolinecarboxylate (**835**, $R = OH$) in 87% yield. The linear tricyclic compound (**835**, $R = OH$) was obtained in 68% yield in polyphosphate at 110–120°C for 1 hr [72JCS(P1)173] in 95% yield on the action of polyphosphate in xylene at 138°C for 2 hr (73GEP2227743) or in 97% yield, in the absence of a solvent, in polyphosphate at 90–100°C for 2 hr (76JAP86497). The ring closure of *N*-(3,4-methylenedioxyphenyl)aminomethylenemalonate (**258**) in phosphoryl chloride at 95–100°C for 4 hr afforded chloro-1,3-dioxino[*g*]quinolinecarboxylate (**835**, $R = Cl$) in 97% yield [71GEP2033971, 71JHC357; 76JAP(K)18440]. The ^{14}C -labeled *N*-(3,4-methylenedioxyphenyl)aminomethylenemalonate (**258**) gave ^{14}C -labeled 1,3-dioxino[*g*]quinoline-carboxylate (**835**, $R = Cl$) (label in position 7), in 82% yield on the action of phosphoryl chloride in boiling toluene for 8 hr (74MI2).



The chloro derivative (**835**, R = Cl) was also prepared in good yield on the action of phosphoryl chloride in the presence of a catalytic amount of polyphosphoric acid (70MIP2; 77TL4545).

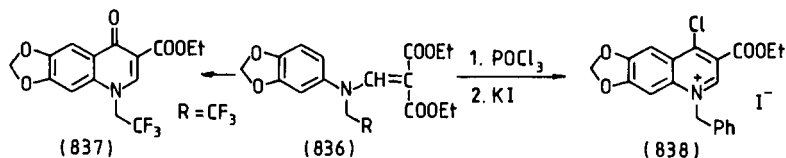
Okumura *et al.* studied the ring closure of *N*-ethyl-*N*-(3,4-methylenedioxyphenyl)aminomethylenemalonate (**286**) in polyphosphoric acid and polyphosphate, which gave the linear tricycle (**755**). The cyclization gave a better yield in polyphosphate than in polyphosphoric acid. Compound **755** was obtained in 78% yield in polyphosphate at 110–120°C for 1 hr, but in only 64% yield in polyphosphoric acid at 120–130°C for 30 min [72JCS(P1)173].

The cyclization of compound **258** in triethyl phosphate at 220°C for 20–30 min in the presence of potassium carbonate, followed by alkaline hydrolysis at 90°C for 1 hr, gave oxolinic acid in 75% yield (70MIP1; 77TL4545). Oxolinic acid was also prepared by reacting 3,4-methylenedioxyaniline and EMME with triethyl phosphate under the previous conditions.

The cyclization of *N*-(2,2,2-trifluoroethyl)-*N*-(3,4-methylenedioxyphenyl)aminomethylenemalonate (**836**, R = CF₃) proceeded smoothly in polyphosphoric acid at 115–120°C for 25 min to give (2,2,2-trifluoroethyl)-1,3-dioxino[*g*]quinoline carboxylate (**837**) (76GEP2534869; 78USP-4086236).

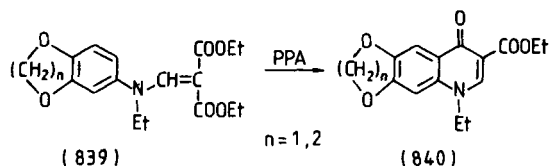
The cyclization of *N*-(3,4-methylenedioxyphenyl)aminomethylenemalonate (**258**) was carried out under acidic conditions by others also (76MIP4).

The cyclization of *N*-benzyl-*N*-(3,4-methylenedioxyphenyl)aminomethylenemalonate (**836**, R = Ph) in refluxing phosphoryl chloride for 7 hr afforded 5-benzyl-8-chloro-1,3-dioxino[*g*]quinolinium iodide (**838**) in 67% yield (71JHC357).

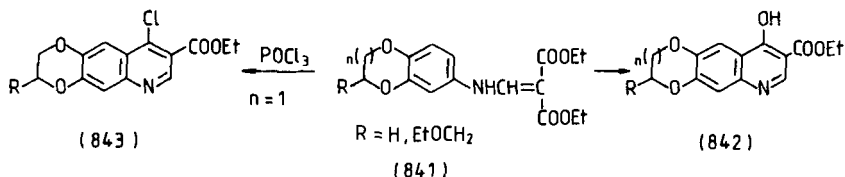


The ring closure of *N*-ethyl-*N*-(3,4-alkylenedioxyphenylamino)methylenemalonates (**839**) in polyphosphoric acid at 120–130°C for 30 min afforded linearly fused tricyclic pyridine-3-carboxylates (**840**) in over 90% yields (73JAP6479).

N-(1,4-Benzodioxan-6-yl)aminomethylenemalonate (**841**, R = H, *n* = 1) and a homologue (**841**, R = H, *n* = 2) were cyclized to 1,4-dioxino[2,3-*g*]quinolinecarboxylate and its homologue (**842**, R = H,

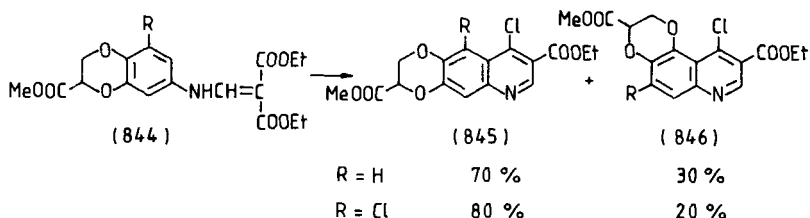


$n = 1, 2$) in good yields by heating in Dowtherm A at 240–150°C for 10–40 min (69FRP2002888; 69GEP1814187, 70GEP1936393; 72BRP1283900; 73GEP2303496; 75KGS1663; 76JMC982). The linearly anelated product (**842**, $R = \text{EtOCH}_2$, $n = 1$) was also obtained when the ring closure of compound **841** ($R = \text{EtOCH}_2$, $n = 1$) was carried out by the action of polyphosphate, prepared from ethanol and phosphorus pentoxide, in boiling xylene for 30 min. In the latter case, when the cyclization was performed in boiling phosphoryl chloride in the presence of a small amount of triethylamine, 9-chloro-1,4-dioxino[2,3-*g*]quinoline-8-carboxylate (**843**, $R = \text{CH}_2\text{OEt}$) was prepared (73GEP2303496).



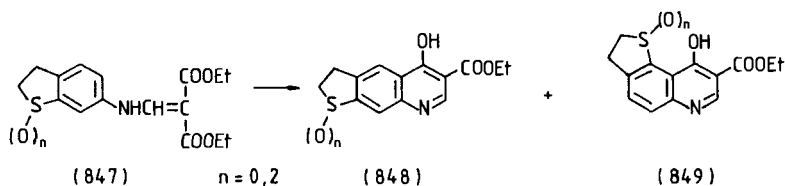
N-(1,4-Benzodioxan-6-yl)aminomethylenemalonate (**841**, $R = \text{H}$, $n = 1$) gave the chloro derivative **843** ($R = \text{H}$) in phosphoryl chloride at 100°C for 2 hr (69GEP1814187).

The cyclization of *N*-(1,4-benzodioxan-6-yl)aminomethylenemalonates (**844**) in boiling phosphoryl chloride for 18 hr afforded a mixture of linear and angular isomeric tricycles (**845** and **846**) in excellent yield (81JOC3846).



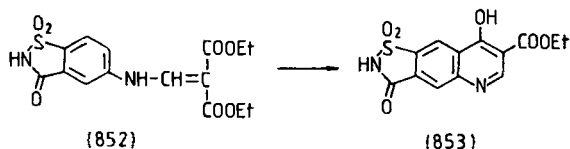
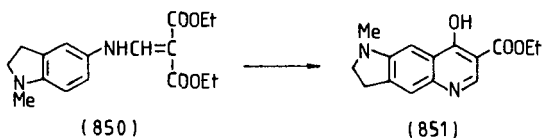
The thermal cyclization of *N*-(2,3-dihydrobenzo[*b*]thien-6-yl)aminomethylenemalonates (**847**, $n = 0, 2$) by heating in boiling Dowtherm A for 35 min and 4 hr gave a roughly 1:1 mixture of thieno[3,2-*g*]quinoline-

6-carboxylates (**848**, $n = 0,2$) and thieno[2,3-*f*]quinoline-8-carboxylates (**849**, $n = 0,2$) in 54% and 83% yields, respectively, while nearly a 4 : 6 mixture of **848** ($n = 2$) and **849** ($n = 2$) was obtained in 26%, following heating in refluxing nitrobenzene for 3 hr (88AP241). Ring closure in polyphosphate at 110–130°C for 2 hr afforded a nearly 1 : 1 mixture of **848** ($n = 2$) and **849** ($n = 2$) in 19% yield or a roughly 6 : 4 mixture of **848** ($n = 0$) and **849** ($n = 0$) in 45% yield.



The thermal ring closure of 5-indolinylinaminomethylenemalonate (**850**) by heating in Dowtherm A at reflux temperature for 20 min afforded the linear pyrrolo[2,3-*g*]quinolinecarboxylate (**851**) in 33% yield (77MI4).

The ring closure of *N*-(1,2-benzisothiazol-5-yl)aminomethylenemalonate 1,1-dioxide (**852**) by heating in diphenyl ether at 250°C gave the linear isothiazolo[5,4-*g*]quinolinecarboxylate (**853**) [74JAP(K)75596].

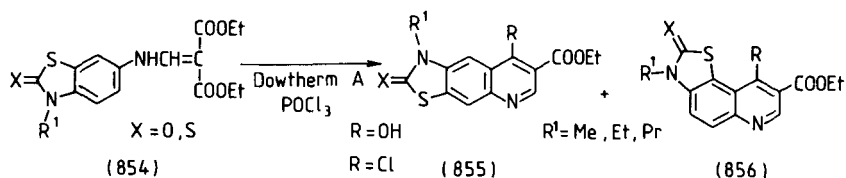


A mixture of linear and angular thiazoloquinolinecarboxylates (**855** and **856**, $R = OH, Cl$ and $X = O$) was obtained on the cyclization of 6-benzothiazolyl)aminomethylenemalonate (**854**, $R^1 = Me$ and $X = O$), either in boiling Dowtherm A or in boiling phosphoryl chloride [75JAP(K)46698].

A 1 : 1 mixture of linear and angular thiazoloquinolinecarboxylates (**855** and **856**, $R = OH, X = O$) in 78–86% yields was obtained by the thermal

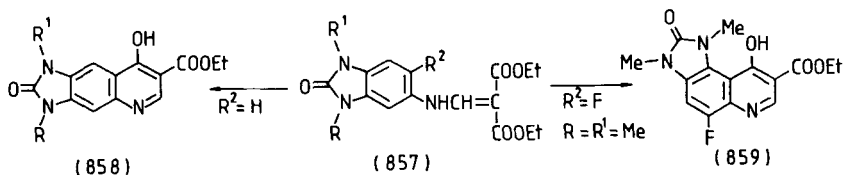
cyclization of 6-benzothiazolylaminomethylenemalonates (**854**, $R^1 = \text{Me}$, Et, Pr, $X = \text{O}$) (76CPB1050).

The ring closure of a thio derivative (**854**, $R^1 = \text{Me}$, $X = \text{S}$) in boiling Dowtherm A gave a 1 : 4 mixture of thiazolo[4,5-*g*]quinoline-6-carboxylate (**855**, $R = \text{OH}$; $R^1 = \text{Me}$; $X = \text{S}$) and thiazolo[5,4-*f*]quinoline-8-carboxylate (**856**, $R = \text{OH}$, $R^1 = \text{Me}$; $X = \text{S}$) in 95% yield (76CPB1050).

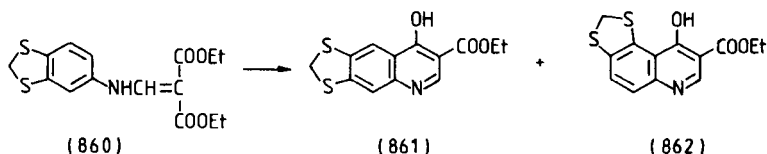


5-Benzimidazolylaminomethylenamalonates (**857**, $R^2 = \text{H}$) were thermally cyclized at 240–245°C for 30 min to give imidazo[4,5-*g*]quinolinecarboxylates (**858**) [78JAP(K)50197].

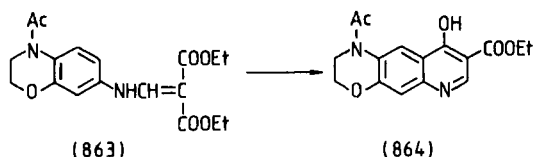
When heated in polyphosphate at 130°C, *N*-(6-fluoro-5-benzimidazolyl)aminomethylenemalonate (**857**, $R = R^1 = \text{Me}$, $R^2 = \text{F}$) gave the angular imidazo[4,5-*f*]quinolinecarboxylate (**859**) in 39% yield [79JAP(K)-144398].



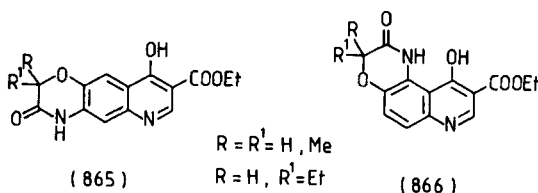
The thermal ring closure of *N*-(1,3-benzodithiol-5-yl)aminomethylenemalonate (**860**) in Dowtherm A at 253–258°C led to a 7.3 : 1 mixture of 1,3-dithiolo[4,5-*g*]quinolinecarboxylate (**861**) and 1,3-dithiolo[4,5-*f*]quinolinecarboxylate (**862**) in 81% yield (86M1339). The cyclization of diethyl *N*-(3,4-dimethylthiophenyl)aminomethylenemalonate under similar conditions afforded only ethyl 6,7-dimethylthio-4-hydroxyquinoline-3-carboxylate.



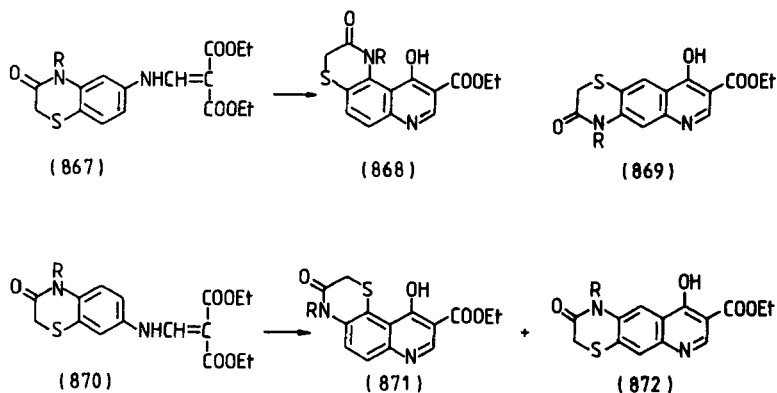
N-(1,4-Benzoxazin-7-yl)aminomethylenemalonate (**863**) was cyclized to the linear pyrido[3,2-*g*]-1,4-benzoxazinecarboxylate (**864**) in 75% yield by heating in Dowtherm A at 250°C for 10 min [78JAP(K)28196].



The ring closure of *N*-(1,4-benzoxazin-6-yl)aminomethylenemalonates (**80**) in boiling diphenyl ether for 30 min gave mixtures of isomeric 1,4-oxazino[2,3-*g*]quinoline-8-carboxylates (**865**) and 1,4-oxazino[3,2-*f*]quinoline-6-carboxylates (**866**) in good yields, with an excess of the linearly anelated ring systems (**865**) [88IJC(B)649].

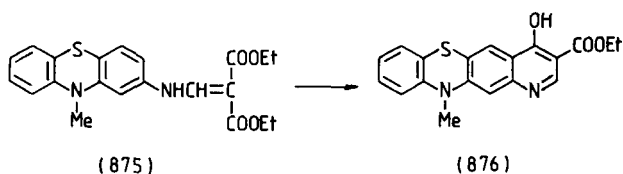
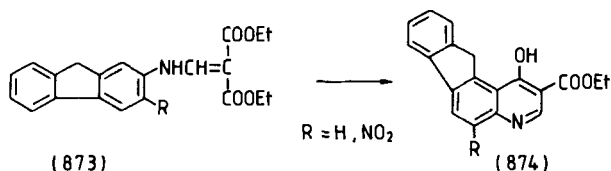


The ring closure of *N*-(1,4-benzothiazin-6- and -7-yl)aminomethylenemalonates (**867** and **870**) by heating in diphenyl ether at 250–270°C for 30 min gave mixtures of angular 1,4-thiazinoquinolinecarboxylates (**868** and **871**) and linear 1,4-thiazinoquinolinecarboxylates (**869** and **872**), with a predominance of the angular isomers (84M16).



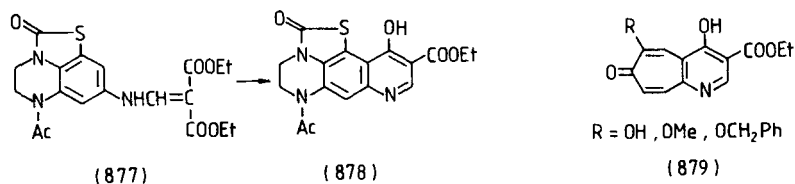
The cyclization of 2-fluorenylaminomethylenemalonates (**873**) by heating in diphenyl ether at 245°C afforded indeno[2,1-*f*]quinoline-2-carboxylates (**874**) in over 95% yield (51JA1844).

2-Phenothiazinylaminomethylenemalonate (**875**) was heated in diphenyl ether for 1 hr at 270°C to give the linear pyrido[2,3-*b*]phenothiazinecarboxylate (**876**) in 79% yield (79JAP(K)30198).



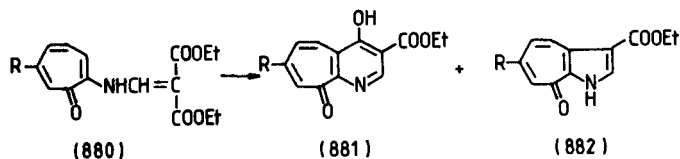
The thermal cyclization of *N*-(thiazolo[4,3,2-*de*]quinoxalin-8-yl)aminomethylenemalonate (**877**) by heating in Dowtherm A at 245°C for 10 min afforded the tetracyclic compound (**878**) in 78% yield [78JAP(K)28196].

N-(5- and 7-oxocycloheptatrien-1-yl)aminomethylenemalonates (**45** and **880**) were cyclized by heating in boiling diphenyl for 8–40 min to give 7- and 9-oxocyclohepta[*b*]pyridines (**879** and **881**) in good yields (83USP4381304,

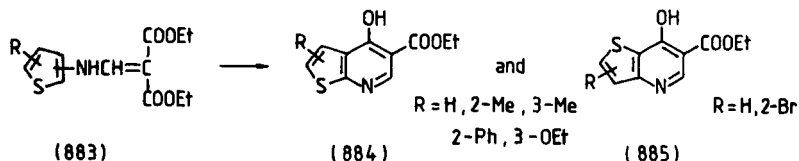


83USP4382088). On the cyclization of *N*-(7-oxocycloheptatrien-1-yl)aminomethylenemalonate (**880**, R = H), cyclohepta[*b*]pyrrole-3-carboxylate (**882**) was isolated as a byproduct (83USP4381304).

The thermal cyclization of 2- and 3-thienylaminomethylenemalonates (**883**) in boiling Dowtherm A or in boiling diphenyl ether for 0.25–1.5 hr

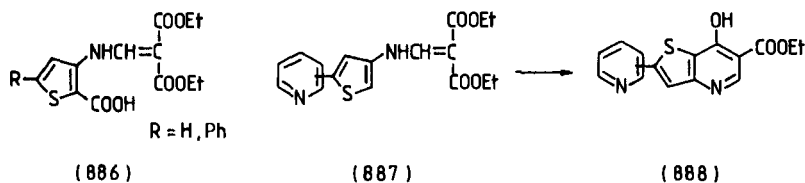


gave thieno[2,3-*b*]pyridines (884) [77JHC807; 78BEP858479] and thieno[3,2-*b*]pyridines (885) [77JHC807; 78BEP858479, 78MI3; 82JCR(M)4701, 82JCR(S)158; 87T3295; 88EUP269295] in 60–84% yields.



During the heating of *N*-(2-carboxy-3-thienyl)aminomethylenemalonates (886, $R = \text{H, Ph}$) in boiling diphenyl ether (88EUP269295) or in polyphosphate [78JCR(M)4701, 78JCR(S)393], the ring closure was accompanied by decarboxylation to thieno[3,2-*b*]pyridines (885, $R = \text{H, 2-Ph}$).

3-Thienylaminomethylenemalonates (887) were cyclized by heating in polyphosphate at 120°C for 2.5 hr to give thieno[3,2-*b*]pyridines (888) [82JAP(K)116077].

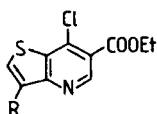


3-Thienylaminomethylenemalonates (58, $R = \text{H, Cl}$) were heated in boiling phosphoryl chloride for 18 hr to afford 7-chlorothieno[3,2-*b*]pyridine-6-carboxylates (889, $R = \text{H, Cl}$) in moderate yields (84EUP126970).

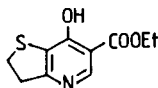
Dichlorothieno[3,2-*b*]pyridine-6-carboxylate (889, $R = \text{Cl}$) was obtained in 65% yield (82EUP46990) when *N*-(5-bromo-3-thienyl)aminomethylenemalonate (58, $R = \text{Br}$) was heated in phosphoryl chloride at 110°C for 3–5 hr. During preparation, the reaction mixture was allowed to cool and was then saturated with hydrogen chloride gas; the temperature of the reaction mixture was again raised to 105–110°C and was stirred for 50 hr at this temperature.

The cyclization of (**58**, R = Br) in phosphoryl chloride at 110°C for 4 hr afforded a 2:3 mixture of 2,7-dichloro- and 2-bromo-7-chlorothieno [3,2-*b*]pyridine-6-carboxylates (**889**, R = Cl and Br) in 82% yield (82EUP46990).

A 1:1 mixture of *N*-(dihydro-3-thienyl)aminomethylenemalonates (**279** and **280**) was heated in Dowtherm A at 250°C for 2 hr to give thieno [3,2-*b*]pyridine-6-carboxylate (**890**) (87USP4647566).

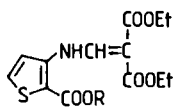


(889)

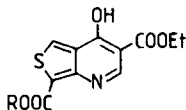


(890)

N-(2-Alkoxy carbonyl-3-thienyl)aminomethylenemalonates (**891**) were stable even under drastic thermal conditions, but were smoothly cyclized in polyphosphate at 130°C to give thieno[3,4-*b*]pyridine-3,6-dicarboxylates (**892**) [80JCR(S)4].



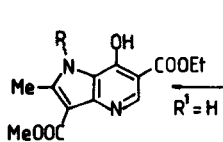
(891)



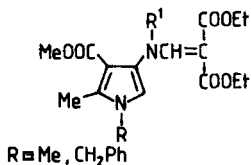
(892)

The cyclization of 3-pyrrolylaminomethylenemalonates (**893**, R¹ = H) was carried out in boiling Dowtherm A for 30–40 min under argon to give pyrrolo[3,2-*b*]pyridine-6-carboxylates (**894**) in 75–87% yields (85JHC83).

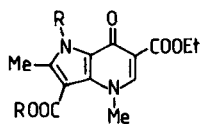
N-Methyl-*N*-(3-pyrrolyl)aminomethylenemalonates (**893**, R¹ = Me) were cyclized by heating in polyphosphate at 95–100°C for 1.5–2.5 hr to afford pyrrolo[3,2-*b*]pyridine-6-carboxylates (**895**) in 50–72% yields (85JHC83).



(894)



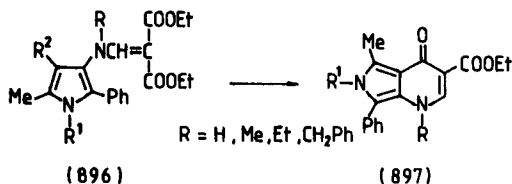
(893)



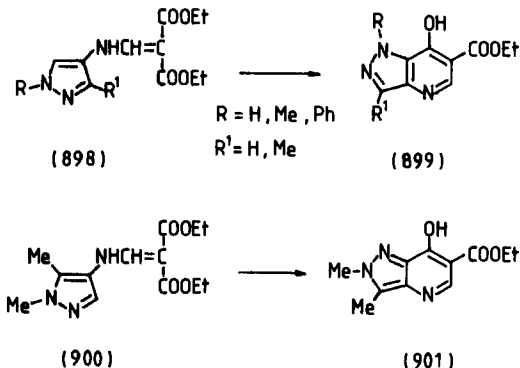
(895)

The cyclization of *N*-(2-phenyl-5-methylpyrrol-3-yl)aminomethylenemalonates (**896**, R = R² = H) in polyphosphate at 100–110°C for 1.5–2.0 hr gave pyrrolo[3,4-*b*]pyridine-6-carboxylates (**897**, R = H) in 70–90%

yields. Pyrrolo[3,4-*b*]pyridinecarboxylate (**897**, $R = R^1 = \text{Me}$) was obtained in 94% yield by cyclization of the 4-carboxylic acid derivative (**896**, $R = R^1 = \text{Me}$; $R^2 = \text{COOH}$) under similar conditions (85JHC729).

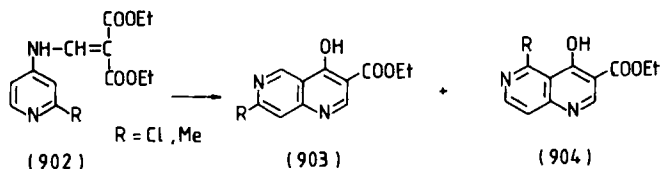


The ring closure of *N*-(5-unsubstituted pyrazol-4-yl)aminomethylenemalonates (**898**) in boiling Dowtherm A for 15 min gave 1*H*-pyrazolo[4,3-*b*]pyridine-6-carboxylates (**899**) in 56–88% yields [76JCS(P1)507; 77JAP(K)77086], but *N*-(1,5-dimethylpyrazol-4-yl)aminomethylenemalonate (**900**) afforded 2*H*-pyrazolo[4,3-*b*]pyridine-6-carboxylate (**901**) in 65% yield under similar conditions [76JCS(P1)507].



Earlier, it was stated that the cyclization of *N*-(2-chloro-4-pyridyl)aminomethylenemalonate (**902**, $R = \text{Cl}$) in diphenyl ether at 250–255°C for 6 min gave 7-chloro-1,6-naphthyridine-3-carboxylate (**903**, $R = \text{Cl}$) (74GEP2362553), but it was later demonstrated that a roughly 3 : 1 mixture of isomeric 7- and 5-chloro-1,6-naphthyridine-3-carboxylates (**903** and **904**, $R = \text{Cl}$) was formed in 57% yield (82CPB2399).

The cyclization of *N*-(2-methyl-4-pyridyl)aminomethylenemalonate (**902**) in boiling Dowtherm A afforded a 1 : 2 mixture of isomeric 7- and 5-methyl-1,6-naphthyridine-3-carboxylates (**903** and **904**, $R = \text{Me}$) in 53% yield (65USP3225055).



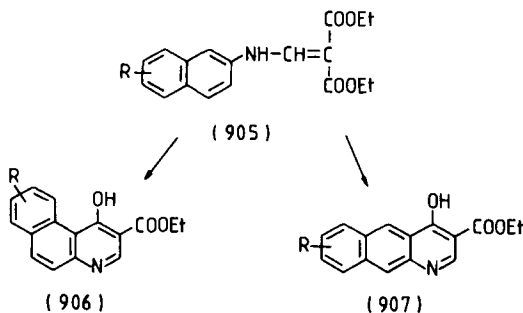
4. CYCLIZATION OF 2-NAPHTHYLAMINOMETHYLENEMALONATES AND RELATED RING SYSTEMS

In the case of 2-naphthylaminomethylenemalonates (905) and related ring systems in which an aromatic moiety is condensed to the benzene ring, linearly and angularly fused isomers may form (Scheme 44). Ring closure in position 1 leads to the angular product (906), while in position 3 it gives the linear isomer (907). According to Clark's theorem (72MI1) and its extension to heterocyclic analogues (84JOC3199), it can be expected that formation of the angularly fused isomer is favored over the linearly fused one because of the higher aromatic stabilization of the former.

The cyclization of 2-naphthylaminomethylenemalonates (905) in a high-boiling solvent (diphenyl ether, Dowtherm A, mineral oil) at 250°C gave the angular isomer (906) in good yields (39JA2890; 46JA1327; 67USP3324003, 67USP3224135).

Heeramanek and Shah obtained 3-phenylbenzo[*f*]quinoline-2-carboxylate (908) in good yield on the ring closure of diethyl phenyl(2-naphthylamino)methylenemalonate by heating in the melt at 185–195°C (37JCS867).

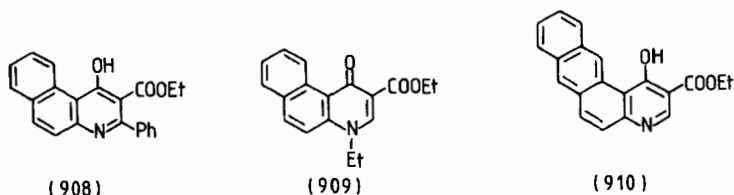
The ring closure of *N*-ethyl-*N*-(2-naphthyl)-aminomethylenemalonate by treatment with an equal amount of phosphorus pentoxide at 130°C



SCHEME 44

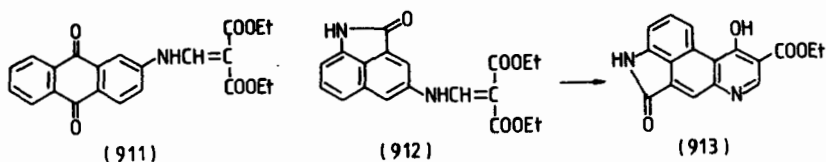
afforded benzo(*f*)quinoline-2-carboxylic acid (**909**) in 41% yield after the work-up process. An exothermic reaction occurred, and the temperature rose to about 190°C. A better yield (76%) was achieved when the reaction was carried out in nitrobenzene (72HCA1319).

The cyclization of 2-anthranylaminomethylenemalonate by heating in diphenyl ether gave naphtho[2,1-*f*]quinolinecarboxylate (**910**) in 96% yield (62MI2).

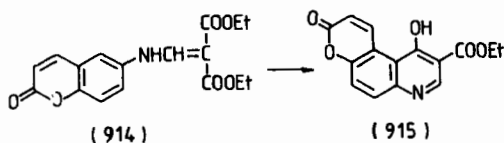


On the cyclization of 2-naphthoquinonylaminomethylenemalonate (**911**) in boiling diphenyl ether, an insoluble product was obtained (59MI2).

3-Naphthostyrylaminomethylenemalonate (**912**) was heated at 250°C to give a tetracyclic compound (**913**) in almost quantitative yield (39JA2890).



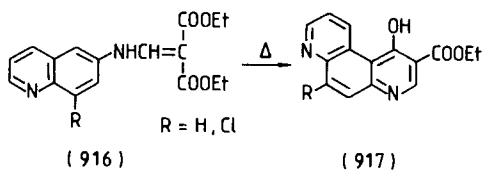
Pyrano[3,2-*f*]quinoline-9-carboxylate (**915**) was obtained in 93% yield by the thermal cyclization of 6-coumarinylaminomethylenemalonate (**914**) in boiling Dowtherm A for 10 min (67USP3313818).



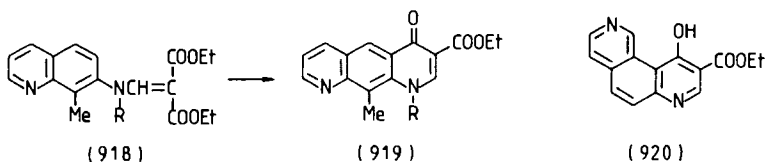
The ring closure of 6-quinolylaminomethylenemalonates (**916**) by heating in mineral oil at 250–260°C for 15 min gave 4,7-phenanthrolinecarboxylate (**917**) in good yield (49JCS1017).

The cyclization of *N*-(8-substituted 7-quinolyl)aminomethylenemalonates (**918**, R = H, Et) in boiling Dowtherm A (R = H¹) for 1 hr or in

polyphosphate ($R^1 = \text{Et}$) at 130°C for 3 hr under nitrogen afforded linear pyrido[3,2-*g*]quinoline-3-carboxylates (**919**) (88M761).

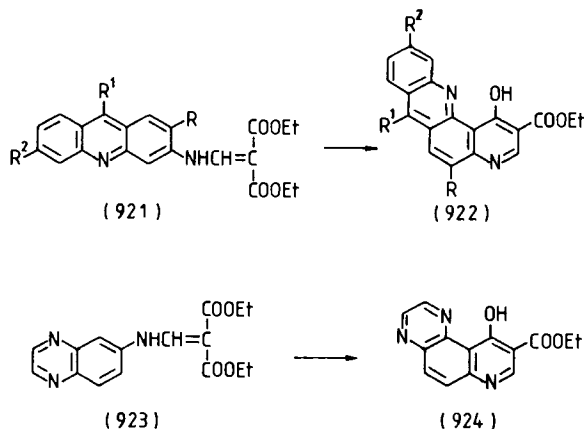


Diethyl 7-isoquinolinylaminomethylenemalonate was cyclized by heating in boiling ether for 20 min to yield the angular 2,7-phenanthrolinecarboxylate (**920**) (81EUP27904).



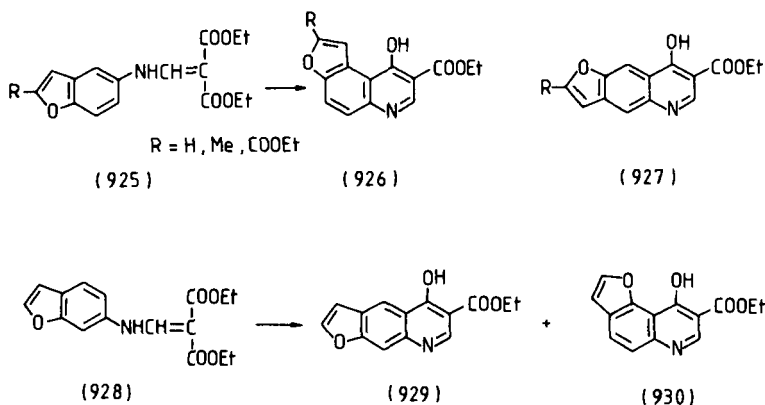
The thermal cyclization of 3-acridinylaminomethylenemalonates (**921**) by heating in diphenyl ether at $260\text{--}270^\circ\text{C}$ for 20 min afforded pyrido[2,3-*c*]acridine-2-carboxylates (**922**) in good yields [77JAP(K)3099, 77USP 4060527].

Diethyl 6-quinoxalylaminomethylenemalonate (**923**) was cyclized by heating in diphenyl ether at $260\text{--}280^\circ\text{C}$ for 1 hr to give pyrido[3,2-*f*]quinoxaline-9-carboxylate (**924**) in 90% yield [78JAP(K)147095; 79GEP2833018].

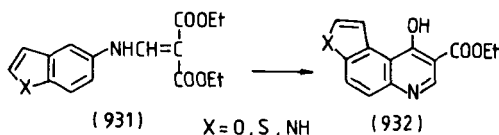


The thermal cyclization of 5-benzofuranylaminomethylenemalonates (**925**) in boiling Dowtherm A afforded angular furo[3,2-*f*]quinolinecarboxylates (**926**) in good yields (70GEP2021100; 78BRP1240446). Earlier, the structure of the products was incorrectly given as **927** (69GEP1908542).

The 6-benzofuranylaminomethylenemalonate (**928**) can be regarded as both a *meta*-alkoxy-substituted and an aromatic ring condensed phenylamine derivative. On thermal ring closure in boiling Dowtherm A for 30 min, a 1 : 1 mixture of furo[3,2-*g*]quinoline-6-carboxylate (**929**) and furo[2,3-*f*]quinoline-8-carboxylate (**930**) was obtained in 70–80% yield (70GEP2021100; 71BRP1240446), indicating that both the alkoxy substituent and the aromatic moiety exerted an influence.

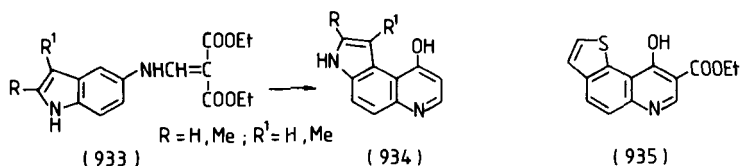


5-Benzfuranyl-, 5-benzothieryl-, and 5-indolylaminomethylenemalonates (**931**, X = O, S, NH) gave the corresponding angular tricyclic quinolinecarboxylates (**932**, X = O, S, NH) in good yields when heated in Dowtherm A (72LA55).

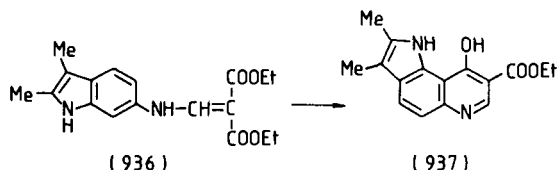


5-Indolylaminomethylenemalonates (**933**) were cyclized by heating in boiling diphenyl ether for 20–40 min to give the angular pyrrolo[3,2-*f*]quinolinecarboxylates (**934**) in 56–68% yields (79KGS1084; 84M12).

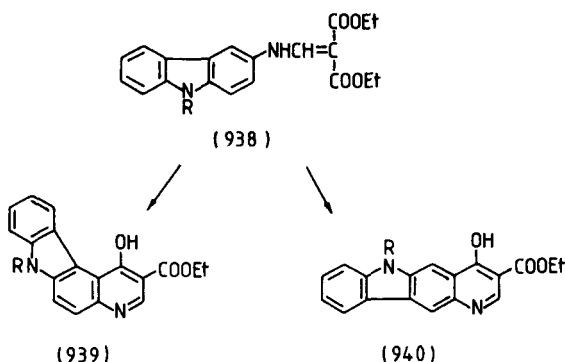
The cyclization of diethyl *N*-(benzo[*b*]thien-6-yl)aminomethylenemalonate yielded the angular thieno[2,3-*f*]quinolinecarboxylate (**935**) (88M15).



6-Indolylaminomethylenemalonate (**936**) was heated in boiling diphenyl ether for 20–40 min to give pyrrolo[2,3-*f*]quinolinecarboxylate (**937**) in 70% yield (79KGS1084).

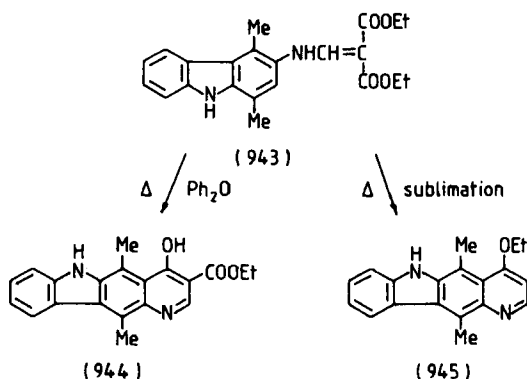
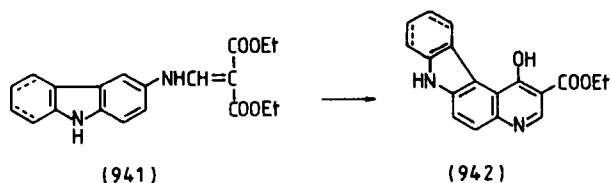


Kulka and Manske cyclized 3-carbazolylaminomethylenemalonates (**938**) in boiling diphenyl ether. They did not decide whether the angular (**939**) or the linear tetracycles (**940**) were formed (52JOC1501).

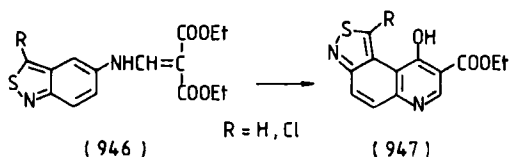


Later, Corelli *et al.* reported that the thermal cyclization of 3-carbazolylaminomethylenemalonates (**941**) by heating in boiling diphenyl ether for 1 hr afforded the angular pyrido[2,3-*c*]carbazolecarboxylates (**942**) in 67–80% yields (87FES641).

If position 4 of the carbazole moiety was substituted, then the linear pyrido[3,2-*b*]carbazole-3-carboxylate (**944**) was obtained in 60% yield in boiling diphenyl ether. The sublimation of compound **943** *in vacuo* at 250°C gave 4-ethoxypyrido[3,2-*b*]carbazole (**945**) in 33% yield (87CPB425).

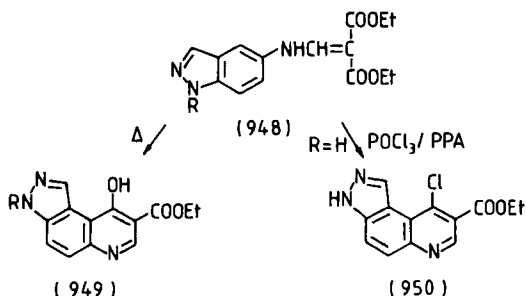


The cyclization of *N*-(2,1-benzisothiazol-5-yl)aminomethylenemalonates (**946**) by heating in diphenyl ether at 250°C for 30 min afforded the angular isothiazolo[4,3-*f*]quinolinecarboxylates (**947**) in good yields [73JAP(K)61500; 74JAP(K)18893; 75JAP(K)84596].



The thermal ring closure of 5-indazolylaminomethylenemalonates (**948**) in Gilotherm at 255°C for 10 min (78GEP2822124) or in diphenyl ether at 250–255°C for 40 min [78YZ1063; 79JAP(K)32496; 80MI3] gave pyrazolo[4,3-*f*]quinolinecarboxylates (**949**) in 40–90% yields.

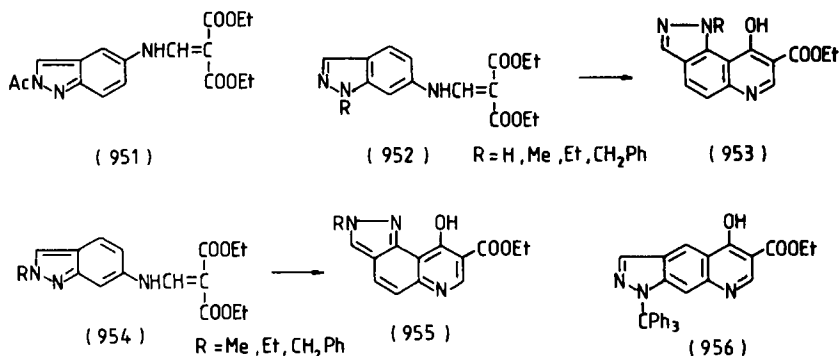
The ring closure of 5-indazolylaminomethylenemalonate (**948**, $R = \text{H}$) in a 6 : 5 mixture of polyphosphoric acid and phosphoryl chloride for 4 hr afforded 9-chloropyrazolo[4,3-*f*]quinoline-8-carboxylate (**950**) in 97% yield [78YZ1063, 79JAP(K)32496].



3-Acetyl-9-hydroxypyrazolo[4,3-*f*]quinoline-8-carboxylate (**949**, R = Ac) was obtained in 64% and 77% yields on the cyclization of both *N*-(1-acetyl- and 2-acetyl-5-indazolyl)aminomethylenemalonates (**948**, R = Ac and **951**) by heating in diphenyl ether at 250–260°C for 35 min and 45 min, respectively [78YZ1063; 79JAP(K)32496].

The cyclization of 6-indazolylaminomethylenemalonates (**952** and **954**) by heating in diphenyl ether or in Gilotherm at 250–270°C gave the angular pyrazolo[3,4-*f*]quinolinecarboxylates (**953** and **955**) in 41–90% yields [77JHC1175; 78GEP2822124, 78JAP(K)119895, 78JAP(K)124299, 78YZ1158; 79USP4160093; 80MI3; 84MI2].

When a bulky substituent was present in position 1 of the indazole moiety (e.g., **952**, R = CPh₃), the linear pyrazolo[4,3-*g*]quinoline-6-carboxylate (**956**) was obtained in 85% yield on thermal cyclization in diphenyl ether at 255–260°C for 40 min [78YZ1158; 79JAP(K)84596]. The angular isomeric pyrazolo[3,4-*f*]quinolinecarboxylate (**953**, R = CPh₃) did not form, probably because of steric reasons (78YZ1158). The cyclization of *N*-(2-trityl-6-indazolyl)aminomethylenemalonate (**954**, R = CPh₃) under similar conditions afforded the angular pyrazolo[3,4-*f*]quinolinecarboxylate (**955**, R = CPh₃) in 44% yield (78YZ1158).



The cyclization of *N*-(1- and 2-trityl-6-indazolyl)aminomethylenemalonates (**952** and **954**, $R = CPh_3$) on the action of a mixture of polyphosphoric acid and phosphoryl chloride for 2 hr gave the angular pyrazolo[3,4-*f*]quinolinecarboxylate (**953**, $R = H$) in 66% and 63% yields, respectively (78YZ1158).

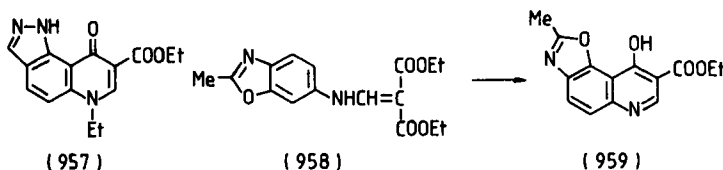
Pyrazolo[3,4-*f*]quinolinecarboxylate (**953**, $R = H$) was also prepared in 67% yield by cyclization of the 1-acetyl derivative of 6-indazolylaminomethylenemalonate (**952**, $R = Ac$) in diphenyl ether at 255–260°C for 0.5 hr (78YZ1158). It was also prepared in 73% yield in a 1 : 3.6 mixture of polyphosphoric acid and phosphoryl chloride at 100°C for 4 hr [77JHC1175; 78JAP(K)124299].

N-(7-Nitro-6-indazolyl)aminomethylenemalonate could not be cyclized by heating in Gilotherm at 250–255°C (80MI3).

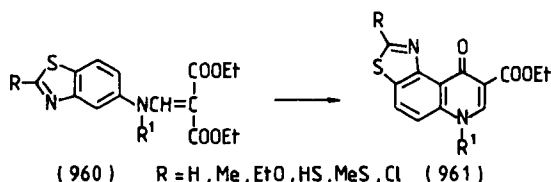
6-Aminoindazole and its 1-benzyl derivative were reacted with EMME in Dowtherm A at 235–245°C for 4.0–6.5 hr to give pyrazolo[3,4-*f*]quinolines (**953**, $R = H$, CH_2Ph) in 38% and 50% yields, respectively (83JHC1351).

The reaction of 6-(ethylamino)indazole and EMME in Dowtherm A at 255°C for 2 hr gave only 2% of 6-ethylpyrazolo[3,4-*f*]quinoline-8-carboxylate (**957**) (83JHC1351).

Cyclization of 6-benzoxazolylaminomethylenemalonate (**958**) by heating in diphenyl ether at 250°C for 1.5 hr afforded the angular oxazolo[5,4-*f*]quinolinecarboxylate (**959**) [74JAP(K)72297].

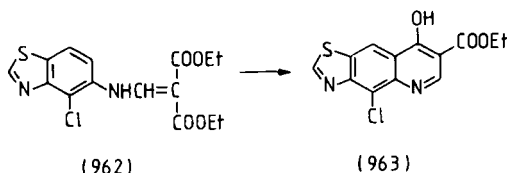


5-Benzothiazolylaminomethylenemalonates (**960**, $R^1 = H$) were heated in boiling diphenyl ether or in boiling Dowtherm A, to give angular thiazolo[4,5-*f*]quinolinecarboxylates (**961**, $R^1 = H$) in 58–93% yields [71GEP2056224, 71GEP2119396; 74JAP(K)88882].



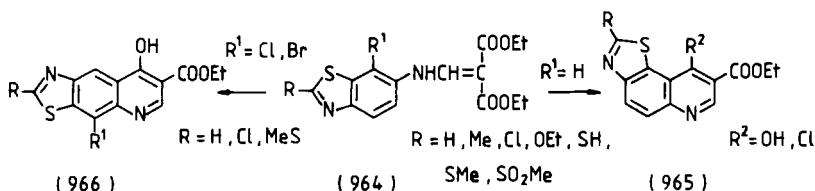
The cyclization of *N*-ethyl-*N*-(5-benzothiazolyl)aminomethylenemalonate (**960**, $R = \text{SMe}$, $R^1 = \text{Et}$) by heating in polyphosphate at 120°C for 15–30 min gave thiazolo[4,5-*f*]quinolinecarboxylate (**961**, $R = \text{SMe}$, $R^1 = \text{Et}$) in 48–63% yields [75JAP(K)52094; 76CPB130].

When position 4 of the 5-benzothiazole moiety (e.g., **962**) was substituted, thermal cyclization in refluxing Dowtherm A for 10–15 min led to the linear thiazolo[5,4-*g*]quinolinecarboxylate (**963**) in 81% yield [77JAP(K)125196; 79CPB1].



The thermal cyclization of 6-benzothiazolylaminomethylenemalonates (**964**, $R^1 = \text{H}$) by heating in Dowtherm A at 250–260°C for 13–40 min afforded the angular thiazolo[5,4-*f*]quinolinecarboxylates (**965**, $R^2 = \text{OH}$) in 59–98% yields (75GEP2449544; 76CPB130). If the heterocyclic ring of 6-benzothiazolylaminomethylenemalonate (e.g., **854**) was not aromatic, the angular thiazolo[5,4-*f*]quinolinecarboxylates (e.g., **856**) were accompanied by the isomeric linear thiazolo[4,5-*g*]quinolinecarboxylates (e.g., **855**) (76CPB1050) (see Section A.3, this chapter).

The ring closure of 6-benzothiazolylaminomethylenemalonates (**964**, $R^1 = \text{H}$) by heating in phosphoryl chloride at 95°C for 3–12 hr gave 9-chlorothiazolo[5,4-*f*]quinoline-8-carboxylate (**965**, $R^2 = \text{Cl}$) in 48–90% yields [73JAP(K)23800; 75GEP2449544, 75JAP(K)64298; 76CPB130]. The hydroxy derivative (**964**, $R = \text{OH}$, $R^1 = \text{H}$) gave dichlorothiazoloquinoline (**965**, $R = R^2 = \text{Cl}$) in 85% yield in phosphoryl chloride (75GEP2449544). The cyclization of *N*-(2-chloro-6-benzothiazolyl)aminomethylenemalonate (**964**, $R = \text{Cl}$, $R^1 = \text{H}$) was carried out by heating in toluene on the action of phosphoryl chloride, in a mixture of phosphoryl chloride and phosphorus trichloride or in a mixture of phosphoryl chloride and phosphorus pentachloride, for 10–12 hr to give 2,9-dichlorothia-

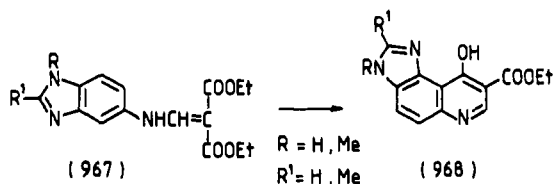


zolo[5,4-*f*]quinoline-8-carboxylate (**965**, $R = R^2 = \text{Cl}$) in 71–77% yields [75GEP2449544, 75JAP(K)64298].

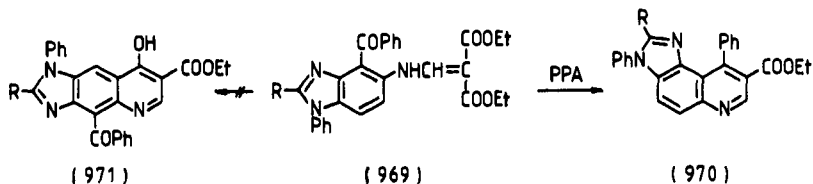
The cyclization of the 2-methylthio derivative (**964**, $R = \text{MeS}$, $R^1 = \text{H}$) was attempted unsuccessfully by heating in polyphosphoric acid, in polyphosphate, or in a mixture of phosphoryl chloride and polyphosphoric acid (76CPB130).

If position 7 of the benzothiazole moiety of 6-benzothiazolylaminomethylenemalonates (**964**, $R^1 = \text{Cl}$, Br) was substituted, then thiazolo[4,5-*g*]quinolinecarboxylates (**966**) were obtained in 61–78% yields in boiling Dowtherm A for 10–15 min [77JAP(K)83596, 77JAP(K)125196; 79CPB1] or in 10% yield in polyphosphate at 120–130°C [77JAP(K)83596, 77JAP(K)125196].

The cyclization of 5-benzimidazolylaminomethylenemalonates (**967**) by heating in boiling Dowtherm A or diphenyl ether for 5–10 min gave imidazo[4,5-*f*]quinolinecarboxylates (**968**) in 52–60% yields [75JHC1319; 80JAP(K)28920; 82MI1; 86EUP187705].

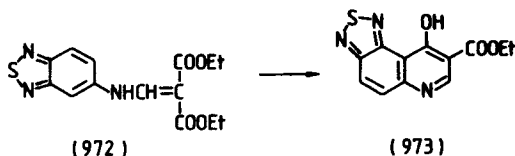


The cyclization of *N*-(1-phenyl-4-benzoyl-5-benzimidazolyl)aminomethylenemalonates (**969**) by heating in polyphosphoric acid afforded 3,9-diphenylimidazo[4,5-*f*]quinolines (**970**) in 89–91% yields, instead of the imidazo[4,5-*g*]quinolines (**971**) (86KGS857).



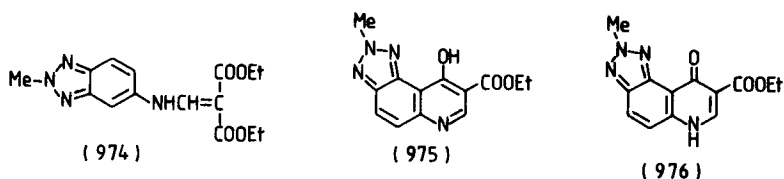
N-(2,1,3-Benzothiadiazol-5-yl)aminomethylenemalonate (**972**) yielded the angularly fused 1,2,5-thiadiazolo[3,4-*f*]quinolinecarboxylate (**973**) when heated in diphenyl ether at 250°C for 30 min [74JAP(K)15498].

N-(1,2,3-Benzotriazol-5-yl)aminomethylenemalonate (**974**) was cyclized by heating in polyphosphoric acid to give 1,2,3-triazolo[4,5-*f*]quino-

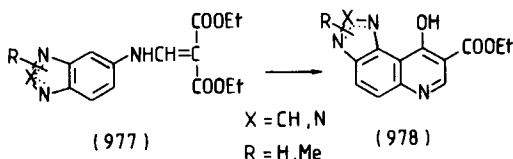


line-3-carboxylate (**975**) (82MI6). The thermal cyclization of **974** gave also the angular ring system (**975**) (88MI11).

Nuvole *et al.* stated that the cyclization of **974** and its desmethyl derivative gave tautomeric 9-hydroxy-1,2,3-triazolo[4,5-*f*]quinoline-8-carboxylates (e.g., **975**) or 9-oxo-6,9-dihydro-1,2,3-triazolo[4,5-*f*]quinoline-8-carboxylates (e.g., **976**, depending on the cyclization conditions (in xylene on the action of polyphosphoric acid (PPA) vs. in DMF on the action of PPA and in Dowtherm A under boiling vs. in polyphosphate (89FES609, 89FES619).



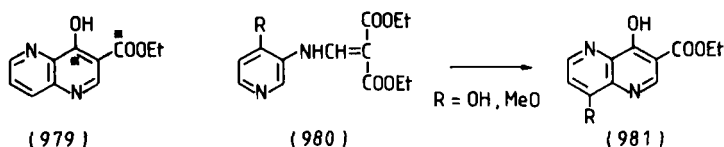
The thermal cyclization of arylaminomethylenemalonates (**977**, R = H, X = CH, N) and their *N*-methyl derivatives (R = Me) in Dowtherm A at 250°C for 15 min afforded the angular tricyclic derivatives (**978**) in excellent yields (87CCC2918; 88MI11; 89CCC713).



5. CYCLIZATION OF 3-PYRIDYLAMINOMETHYLENEMALONATES, THEIR N-OXIDES, AND RELATED SYSTEMS

The ring closure of 3-pyridylaminomethylenemalonates may lead to 1,5-naphthyridine or 1,7-naphthyridine, depending on which position of the pyridine ring (position 2 or 4) is involved in the cyclization (Scheme 45). Due to the higher reactivity of position 2 of 3-aminopyridine derivatives

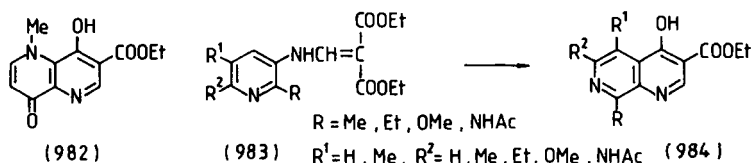
4,8-Dihydroxy- and 4-hydroxy-8-methoxy-1,5-naphthyridine-3-carboxylates (**981**) were prepared in 50% and 72% yields, respectively, by the



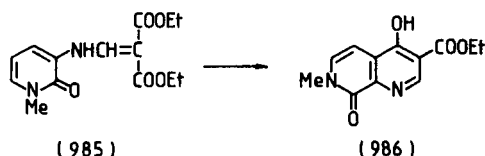
cyclization of *N*-(4-substituted 3-pyridyl)-aminomethylenemalonates (**980**) in boiling diphenyl ether for 25–60 min (71JOC1331; 78JOC1331).

The cyclization of diethyl *N*-(1-methyl-4-oxo-1,4-dihydropyrid-3-yl) aminomethylenemalonate by heating in boiling Dowtherm A for 15 min afforded 1,5-naphthyridine-3-carboxylate (**982**) in 35% yield (78JOC1331).

When position 2 of the pyridine moiety of 3-pyridylaminomethylenemalonates (**983**) was substituted, the thermal ring closure occurred in position 4 to yield 4-hydroxy-1,7-naphthyridine-3-carboxylates (**984**) (66BRP1022214; 69USP3429887; 70BRP1182369, 70USP3506668, 70USP 3517014; 84EUP115469).

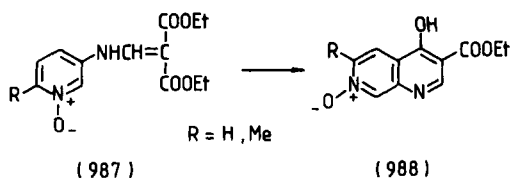


The ring closure of *N*-(1-methyl-2-oxo-1,4-dihydropyrid-3-yl)amino-methylenemalonate (**985**) in refluxing Dowtherm A for 25 min under nitrogen gave 1,7-naphthyridine-3-carboxylate (**986**) in 83% yield (81JHC941).



1,7-Naphthyridine-3-carboxylate derivatives (**988**) were the products when the *N*-oxides of 3-pyridylaminomethylenemalonates (**987**) were applied. The cyclizations were carried out in boiling diethyl phthalate or Dowtherm A (54JOC2008; 66BRP1022214; 69USP3429887; 70USP-3506668).

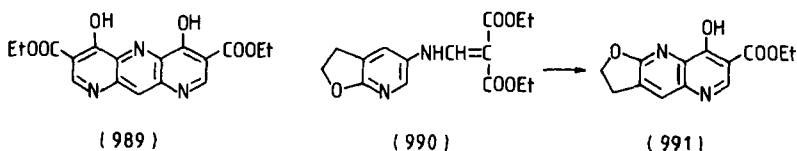
Ethyl 4-chloro-7-methoxy-1,5-naphthyridine-3-carboxylate was prepared in 62% yield by the cyclization of diethyl *N*-(5-methoxy-3-



pyridyl)aminomethylenemalonate in boiling phosphoryl chloride for 5 hr (77GEP2607012).

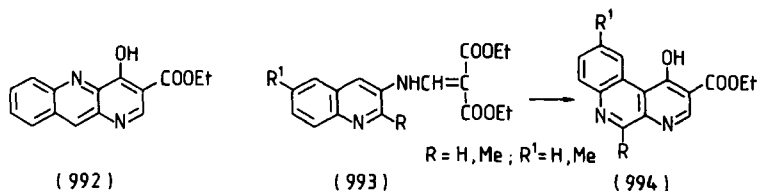
The cyclization of 3,5-bis(aminomethylenemalonate) (**171**) by heating in Dowtherm A for 45 min afforded pyrido[3,2-*b*]-1,5-naphthyridine-3,7-dicarboxylate (**989**) in 81% yield (78BAP509).

The thermal ring closure of *N*-(furo[2,3-*b*]pyridin-5-yl)aminomethylenemalonate (**990**) in boiling Dowtherm A for 12 min afforded furo[2,3-*g*]-1,5-naphthyridinecarboxylate (**991**) in 77% yield (77MI6).



Hauser and Reynolds reported that the reaction of 3-aminoquinoline and EMME in boiling Dowtherm A for 30 min gave the linearly fused benzo[*b*]-1,5-naphthyridinecarboxylate (**992**) in 22% yield (50JOC1224).

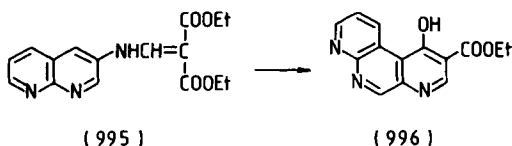
Later, Leshar stated that the ring closure of 3-quinolylaminomethylenemalonates (**993**) by heating in Dowtherm A at 245°C for 20 min afforded the angular benzo[*f*]-1,7-naphthyridinecarboxylates (**994**) (67USP-3300499).



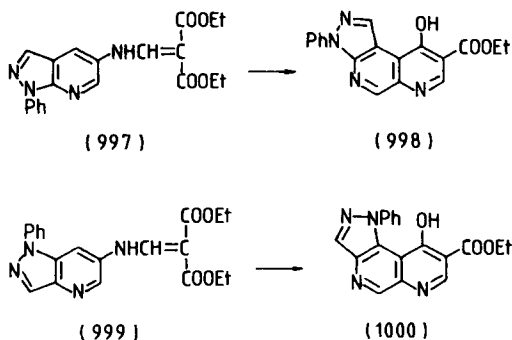
Murakami and Takshima claimed that the thermal cyclization of 3-quinolylaminomethylenemalonate (**993**, $R = R' = H$) gave the linear tricyclic (**992**) (72JAP35919).

In another case, when an aromatic ring was joined to the pyridine ring, the cyclization took place at position 4 of the pyridine moiety to give the angular isomer (*vide infra*).

The cyclization of *N*-(1,8-naphthyridin-3-yl)aminomethylenemalonate (**995**), by heating in refluxing Dowtherm A for 10 min, afforded the angular 1,8,9-triazaphenanthrene-3-carboxylate (**996**) in 93% yield (78YZ1279).



The ring closure of *N*-(pyrazolo[3,4-*b*]pyridin-5-yl)- and *N*-(pyrazolo[4,3-*b*]pyridin-6-yl)aminomethylenemalonates (**997** and **999**) in boiling Gilotherm for 10 min gave the angular tricycles (**998** and **1000**) in 75% and 54% yields, respectively (81M11).

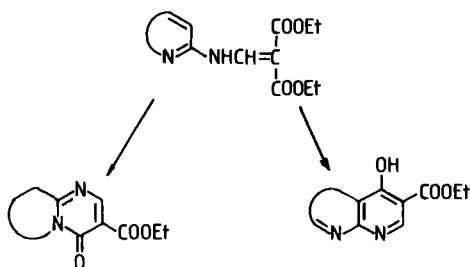


6. CYCLIZATION OF *N*-(α -*N*-HETEROCYCLIC)AMINOMETHYLENEMALONATES

The ring closure of *N*-(α -*N*-heterocyclic)aminomethylenemalonates may lead to the formation of nitrogen bridgehead pyrimidinones when the ring nitrogen is involved in the cyclization. Ring closure may also lead to the formation of condensed pyridines when the ring carbon is involved (Scheme 46).

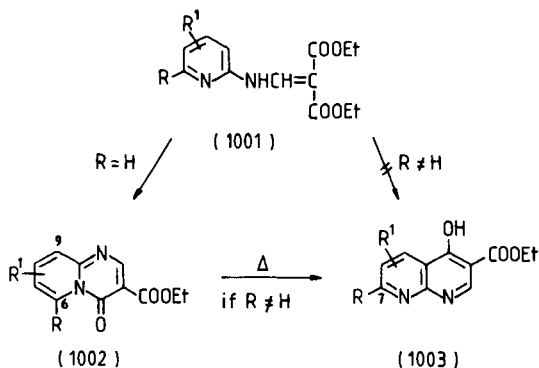
a. Cyclization of 2-Pyridylaminomethylenemalonates

From a study of the thermal ring closure of 2-pyridylaminomethylenemalonates (**1001**) by heating in diphenyl ether, Lappin found that pyrido[1,2-*a*]pyrimidine-3-carboxylates (**1002**) were formed from those malo-



SCHEME 46

nates that did not contain a substituent at position 6 of the pyridine ring (**1001**, $R = H$), while 6-substituted derivatives ($R \neq H$) gave 1,8-naphthyridine-3-carboxylates (**1003**, $R \neq H$) (48JA3348). The formation of 1,8-naphthyridines (**1003**) was due to the presence of a substituent at position 6 of the pyridine moiety of 2-pyridylaminomethylenemalonate (**1001**, $R \neq H$) that sterically inhibited the ring closure on the neighboring ring nitrogen and at the same time activated position 3 for cyclization.



Shur and Israelstam carried out the cyclization of 2-pyridylaminomethylenemalonates (**1001**) in polyphosphoric acid at 110°C for 4 hr (68JOC3015). They reported that pyrido[1,2-*a*]pyrimidine-3-carboxylates (**1002**) were obtained, even if they started from *N*-(6-methyl- or 4,6-dimethyl-2-pyridyl)aminomethylenemalonates (**1001**, $R = \text{Me}$, $R^1 = \text{H}$, 4-Me). However, it was later demonstrated that, in the case of the 6-methyl derivative (**1001**, $R = \text{Me}$, $R^1 = \text{H}$), instead of the pyrido[1,2-*a*]pyrimidine-3-carboxylate (**1002**, $R = \text{Me}$, $R^1 = \text{H}$), the ethyl, hydrogen *N*-(6-methyl-2-pyridyl)aminomethylenemalonate (**378**, $R = \text{Me}$) was probably obtained. The latter

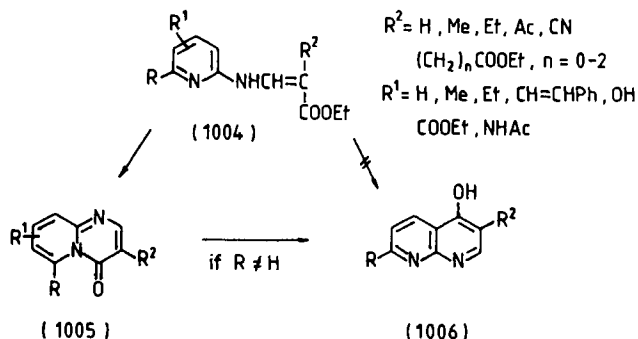
might be formed under the work-up conditions by the hydrolysis of 6-methylpyrido[1,2-*a*]pyrimidine-3-carboxylate (**1002**, $R = \text{Me}$, $R^1 = \text{H}$) (72AF815). Attempted cyclization of the 6-amino derivative (**1001**, $R = \text{NH}_2$, $R^1 = \text{H}$) afforded only tar (68JOC3015).

Hermecz, Mészáros and their co-workers investigated the ring closure of 2-substituted 3-(2-pyridylamino)acrylates (**1004**) and pointed out that the cyclization of 6-substituted 2-pyridyl derivatives (**1001**, **1004**, $R \neq \text{H}$) also gave pyrido[1,2-*a*]pyrimidines (**1002**, **1005**, $R \neq \text{H}$) in the first step, but the nitrogen bridgehead compounds (**1002**, **1005**, $R \neq \text{H}$) could transform to 1,8-naphthyridines (**1003**, **1006**) under thermal conditions (e.g., in a high-boiling solvent above 200°C) [75TL1019; 77JCS(P1)789]. The thermal ring transformation of 6-substituted pyrido[1,2-*a*]pyrimidines (**1002**, **1005**, $R \neq \text{H}$) is facilitated by the steric interaction that exists between the neighboring substituents in *peri* positions 4 and 6. The ring transformation of 6-substituted pyridopyrimidines (**1002**, **1005**, $R \neq \text{H}$) is influenced by the nature of the substituents at both position 6 and position 3 on the pyridopyrimidine skeleton [88JCS(P2)1287]. The nature of the substituent at position 3 primarily determines the bond length between ring atoms C(4) and N(5), while the nature of the substituent at position 6 controls the dihedral angle between the substituents at positions 4 and 6.

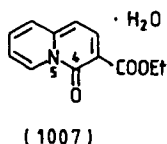
Unsubstituted pyrido[1,2-*a*]pyrimidin-4-ones (**1002**, **1005**, $R = \text{H}$) could not be transformed even under fairly drastic conditions [77JCS(P1)789].

With respect to R^2 (the substituent at position 3 of pyridopyrimidine), the transformation is influenced in the following sequence: $\text{Me} \leq \text{CH}_2\text{COOEt} < \text{H} < \text{Ph} < \text{CN} \leq \text{COCH}_3 \leq \text{COCF}_3 \approx \text{COOEt}$; while with respect to R (the substituent at position 6), the following sequence applies: $\text{COOEt} \approx \text{OH} < \text{alkyl} < \text{styryl} < \text{NHAc}$ [77JCS(P1)789; 78TH1; 80JCS(P1)227].

Further investigation of the thermal ring transformation revealed that the length of the bond between C(4) and N(5), which must break in the



first step during the ring transformation, is influenced primarily by the resonance effect of the substituent at position 3 [88JCS(P2)1287]. Table VII shows X-ray diffraction data on some pyrido[1,2-*a*]pyrimidines and a quinazoline (**1007**). These data indicate that the length of the C(4)—N(5) bond is independent of the properties of the substituent at position 6. Very similar bond lengths were determined by X-ray investigations, for example, for pyrido[1,2-*a*]pyrimidines (**1005**, R = H, Me, R¹ = H, R² = CH₂COOEt) and for compounds **1005** (R = COOEt, R¹ = H, R² = Me) and **1007**, in spite of the fact that the latter is a quinolizine derivative.



However, if we also take into consideration the dihedral angle between group R and the oxygen atoms at positions 6 and 4, it can be observed that bicyclic ring systems not containing a substituent at position 6 (**1005**, R = H; and **1007**) are nearly planar, while in the 6-substituted derivatives (**1005**, R ≠ H), the 4-oxo group and the substituent at position 6 are twisted out of the plane of the bicycle. A larger dihedral angle is associated with a shorter C(4)—N(5) bond [88JCS(P2)1287].

This type of ring transformation occurs not only for pyrido[1,2-*a*]pyrimidines and in the cyclization of 2-pyridylaminomethylenemalonates, but also for other similar ring systems and (hetarylamino)methylenemalonates [e.g., 77JCS(P1)789; 84JCS(P1)1795; also see later].

TABLE VII
CHARACTERISTIC BOND LENGTH AND DIHEDRAL ANGLE DATA ON PYRIDO[1,2-*a*]PYRIMIDINES (**1005**)
AND QUINOLIZINE (**1007**)

| Compound | R | R ¹ | R ² | C(4)—N(5) Bond distance (pm) | Dihedral angle O=C(4) ... C(6)R/° | References |
|-------------------------------|----|----------------|-----------------------|---------------------------------|--------------------------------------|---------------|
| (1005a) | H | H | CH ₂ COOEt | 143.4(4) | 3(2) | 88JCS(P2)1287 |
| (1005b) | Me | H | CH ₂ COOEt | 144.2(3) | 40.4(1) | 88JCS(P2)1287 |
| (1005c) ^a | Me | H | COOEt | 146.9(7) | 29(1) | 72AX(B)2405 |
| | | | | 147.4(7) | 19(1) | |
| (1007) | | | | 146.8(2) | 2.9(8) | 88H385 |

^a Two independent molecules are present in the unit cell.

Cyclization of diethyl *N*-(5-aminocarbonyl-2-pyridyl)aminomethylenemalonate (**1001**, $R = H$, $R^1 = 5\text{-CONH}_2$) in refluxing diphenyl ether for 2 hr gave 1,8-naphthyridine (**1003**, $R = H$, $R^1 = 6\text{-CONH}_2$) in 48% yield (72JMC1203). Later, it was proved that the product was a pyrido[1,2-*a*]pyrimidine (**1002**, $R = H$, $R^1 = 7\text{-CONH}_2$) [77JCS(P1)789].

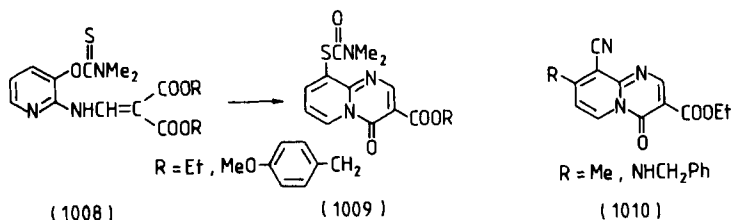
Pyrido[1,2-*a*]pyrimidine-3-carboxylate (**1002**, $R = R^1 = H$) was prepared in 94% and 40% yields by the thermal cyclization of 2-pyridylaminomethylenemalonate (**1001**, $R = R^1 = H$) in boiling diphenyl ether (52JA5491; 77GEP2648770; 80MIP2).

Further pyrido[1,2-*a*]pyrimidine-3-carboxylates (**1002**, $R = H$, $R^1 \neq H$) were prepared by the thermal cyclization of *N*-(6-unsubstituted 2-pyridyl)aminomethylenemalonates (**1001**, $R = H$, $R^1 \neq H$) by heating in a high-boiling solvent [71IJC201, 71JCS(C)2735; 89TL1529].

The cyclization of *N*-(3-hydroxy-2-pyridyl)aminomethylenemalonate (**1001**, $R = H$, $R^1 = 3\text{-OH}$) in Dowtherm A at 220°C for 15 min gave 9-hydroxypyrido[1,2-*a*]pyrimidine-3-carboxylate (**1002**, $R = H$, $R^1 = 9\text{-OH}$) in 29–52% yields. 9-Hydroxypyrido[1,2-*a*]pyrimidine (**1002**, $R = H$, $R^1 = 9\text{-OH}$) was also obtained in 78–93% yields when 2-amino-3-hydroxypyridine was reacted with EMME in diethylbenzene at 140°C for 1–2 hr and then at 180°C for 1–2 hr (73GEP2318821; 75JHC427; 76USP3960847).

The ring closure of 2-pyridylaminomethylenemalonates (**1008**) in boiling diphenyl ether for 10–90 min afforded pyrido[1,2-*a*]pyrimidines (**1009**) in 52–57% yields (85EUP218423).

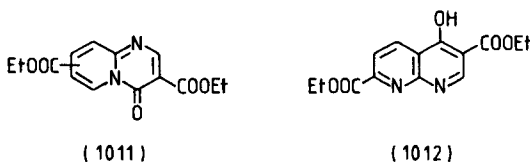
Pyrido[1,2-*a*]pyrimidine-3-carboxylate (**1010**, $R = \text{Me}$) was prepared in 90% yield on the cyclization of diethyl *N*-(3-cyano-4-methyl-2-pyridyl)aminomethylenemalonates by heating in Dowtherm A at 255°C for 1.5 hr (84KGS799).



2-Amino-3-cyano-4-benzylaminopyridine was reacted with EMME in boiling DMF for 6 hr to give pyrido[1,2-*a*]pyrimidine-3-carboxylate (**1010**, $R = \text{NHCH}_2\text{Ph}$) in 35% yield (83KGS816).

The cyclization of *N*-(ethoxycarbonyl-2-pyridyl)aminomethylenemalonates (**49**) was carried out in Dowtherm A at 250–255°C for 0.5 hr to afford

pyrido[1,2-*a*]pyrimidine-3,6-, -3,7-, -3,8-, and -3,9-dicarboxylates (**1011**) in 48–98% yields (79BEP873195; 85JHC481). In the case of the 6-ethoxycarbonyl derivative (**49**, 6-COOEt), 1,8-naphthyridine-3,7-dicarboxylate (**1012**) was also isolated in 7% yield from the reaction mixture.

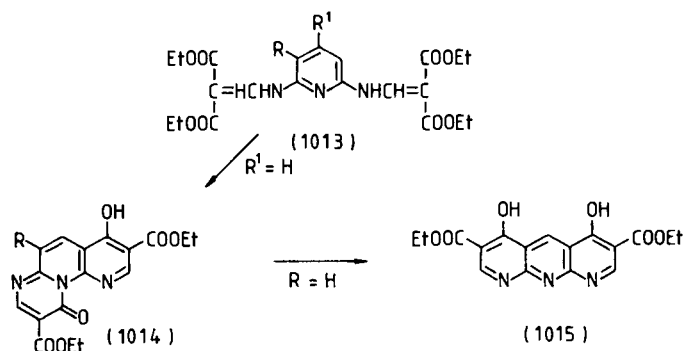


De Fonseca stated that 1,8-naphthyridine (**1003**) was obtained not only from *N*-(6-methyl-2-pyridyl)aminomethylenemalonate (**1001**, $R = \text{Me}$, $R^1 = \text{H}$), but also from 2-pyridylaminomethylenemalonate (**1001**, $R = R^1 = \text{H}$) by thermal cyclization in diethyl phthalate at 280°C (78MI1). This statement seems to be in opposition to the results of earlier investigations, where only pyrido[1,2-*a*]pyrimidine-3-carboxylate (**1002**, $R = R^1 = \text{H}$) was obtained from the 2-pyridyl derivative (**1001**, $R = R^1 = \text{H}$) under thermal conditions [52JA5491; 77GEP2648770, 77JCS(P1)789].

Adams *et al.* reported that when 2,6-diaminopyridine was reacted with an equimolar ratio of EMME in Dowtherm A at 155°C, the temperature of the reaction mixture was then raised to reflux, and the mixture was heated for 1 hr, 1,8-naphthyridine (**1003**, $R = \text{NH}_2$, $R^1 = \text{H}$) was formed (46JA1317).

When *N*-(6-amino-2-pyridyl)aminomethylenemalonate (**1001**, $R = \text{NH}_2$, $R^1 = \text{H}$) was heated in a 1 : 1 mixture of acetic anhydride and Dowtherm A, 7-acetamido-1,8-naphthyridine-3-carboxylate (**1003**, $R = \text{NHAc}$, $R^1 = \text{H}$) was obtained (62BEP612258). This product (**1003**, $R = \text{NHAc}$, $R^1 = \text{H}$) was also prepared in 58% yield, by the cyclization of *N*-(6-acetamido-2-pyridyl)aminomethylenemalonate (**1001**, $R = \text{AcNH}$, $R^1 = \text{H}$) in boiling Dowtherm A for 15 min, and in 88% yield in the reaction of 2-amino-6-acetamidopyridine and EMME under similar conditions (71G129).

The thermal ring closure of bis(aminomethylenemalonate) (**1013**, $R = R^1 = \text{H}$) in boiling Dowtherm A for 10–15 min gave pyrimido[1,2-*a*]-1,8-naphthyridine (**1014**, $R = \text{H}$) [71G129, 71JCS(C)2985], but anthyridine (**1015**) was obtained in 74% yield when compound **1013** ($R = R^1 = \text{H}$) was heated in diphenyl ether for 6 hr [70JHC875; 77JCS(P1)789]. Anthyridine (**1015**) was also obtained from **1013**, ($R = R^1 = \text{H}$) on heating in diphenyl ether at 270°C (84MI4). Pyrimidonaphthyridine (**1014**, $R = \text{H}$) could be



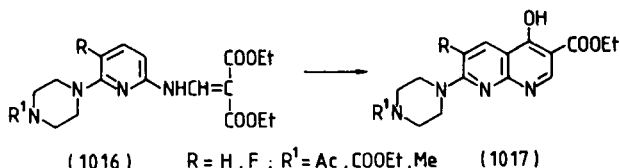
thermally transformed to anthyridine (**1015**) in 80% yield in Dowtherm A at 250–255°C for 6 hr [77JCS(P1)789].

Harper and Wibberley failed to cyclize the 4-ethoxy derivative of compound **1013** ($R = H$, $R^1 = OEt$) under similar conditions [71JCS(C)2985].

The cyclization of bis(aminomethylenemalonate) (**1013**, $R = NO_2$, $R^1 = H$) in boiling Dowtherm A for 30 min afforded pyrimido[1,2-*a*]-1,8-naphthyridine (**1014**, $R = NO_2$) in good yield (72G253).

The thermal ring closure of *N*-(5-nitro-6-diethylamino-2-pyridyl)aminomethylenemalonate (**1001**, $R = Et_2N$, $R^1 = 5-NO_2$) by heating in boiling Dowtherm A for 10 min gave 1,8-naphthyridine (**1003**, $R = Et_2N$; $R^1 = NO_2$) in 51% yield (79YZ155).

1,8-Naphthyridines (**1017**) were obtained in good yields on cyclization of *N*-(6-piperazino-2-pyridyl)aminomethylenemalonates (**1016**) by heating in Dowtherm A [74GEP2362553; 80EUP9425; 81JAP(K)46811; 82FRP-2496663; 84JHC673].



The ring closure of *N*-[6-(4-acetyl-1-piperazinyl)-5-fluoro-2-pyridyl]aminomethylenemalonate (**1016**, $R = F$, $R^1 = Ac$) afforded 1,8-naphthyridine (**1017**, $R = F$, $R^1 = Ac$) in 61% yield on heating in Dowtherm A at 248–250°C for 13 min, and in 96% yield on heating in tridecane at 230–232°C for 5 hr (84JHC673).

The cyclization of *N*-(5-fluoro-6-pyrrolo-2-pyridyl)aminomethylene-

malonate (**1001**, R = pyrrolidino; R¹ = 5-F) by heating in Dowtherm A for 13 min gave 1,8-naphthyridine (**1003**, R = pyrrolidino; R¹ = 6-F) in 76% yield (84JHC673).

The cyclization of *N*-(6-chloro-2-pyridyl)aminomethylenemalonate (**1001**, R = Cl, R¹ = H) by heating in diphenyl ether at 250°C for 20 min gave 1,8-naphthyridine (**1003**, R = Cl, R¹ = H) in 91% yield (82CPB2399).

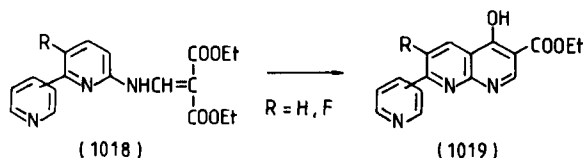
7-Alkyl-1,8-naphthyridine-3-carboxylates (**1003**, R = alkyl) were prepared in good yields on the thermal cyclization of *N*-(6-alkyl-2-pyridyl)aminomethylenemalonates (**1001**, R = alkyl) by heating in a high-boiling solvent (62BEP612258; 66MI1; 68USP3404153; 69CPB1832; 70BRP1208279; 76MIP5, 76NEP3192; 78GEP2811483; 80MIP1; 82MI5; 84AJC1065; 87JHC215).

N-(6-Methyl-2-pyridyl)aminomethylenemalonate (**1001**, R = Me, R¹ = H) was cyclized to 1,8-naphthyridine (**1003**, R = Me, R¹ = H) in 70% yield in a continuous-operation wiped-film reactor with control of the residence time, whereas in a conventional wiped-film reactor, the yield was 25–30% (79MI2). On heating in dodecylbenzene or in diethyl phthalate at 285–300°C for 3–6 min, the yield was 90% (73MIP3).

The cyclization of diethyl *N*-(6-methyl-2-pyridyl)aminomethylenemalonate (**1001**, R = Me, R¹ = H) and of diethyl arylaminomethylenemalonates (**757**, R = R¹ = H, OMe, OCH₂O; R = Cl, R¹ = H) was carried out in dibenzylbenzene at 300–335°C for 1–12 min to give 1,8-naphthyridine (**1003**, R = Me, R¹ = H) and quinoline-3-carboxylates (**759**, R = R¹ = H, OMe, OCH₂O; R = Cl, R¹ = H), respectively, in good yields (74BEP819195; 75GEP2343462).

1,8-Naphthyridines (**1003**, R = Me, 6-R¹ = MeO, EtO, PhCH₂O, MeOCH₂O) were prepared in good yields on the cyclization of *N*-(6-methyl-5-alkoxy-2-pyridyl)aminomethylenemalonates (**1001**, R = Me, 5-R¹ = MeO, EtO, PhCH₂O, MeOCH₂O) by heating in boiling Dowtherm A for 1 hr [79GEP2906253; 80JAP(K)130980; 81CP1114822, 81JAP(K)-131583; 84CPB4914].

The ring closure of *N*-[6-(pyridyl)-2-pyridyl]aminomethylenemalonates (**1018**) by heating in boiling diphenyl ether or Dowtherm A afforded 1,8-naphthyridines (**1019**) in good yields [72GEP2125310; 73BRP1322318, 73FRP2138216; 84FRP2531084; 85JAP(K)112790; 87JMC1622].

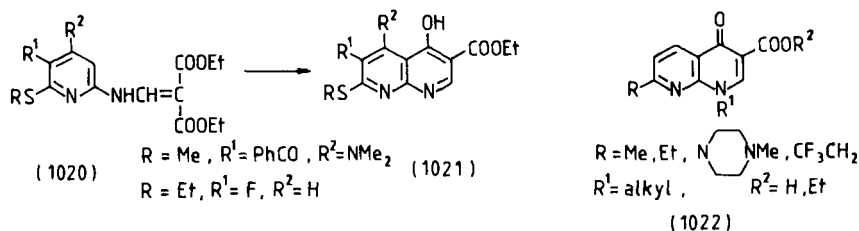


2,5-Dihydroxy-1,8-naphthyridine was prepared in 50% yield by the cyclization of *N*-(6-hydroxy-2-pyridyl)aminomethylenemalononic acid in boiling diphenyl ether for 9 hr (84AJC1065).

The thermal cyclization of *N*-(6-alkylthio-2-pyridyl)aminomethylenemalonate (**1020**) afforded 1,8-naphthyridines (**1021**) in good yields (78KGS1671; 82FRP2500833; 84JHC673).

Shvo and Israelstam obtained pyrido[1,2-*a*]pyrimidine-3-carboxylate (**1002**, $R = R^1 = H$), when 2-aminopyridine was reacted with EMME in polyphosphoric acid at 110–120°C for 2–3 hr (68JOC3015).

The cyclization of diethyl *N*-substituted *N*-(6-alkyl-2-pyridyl)aminomethylenemalonates (**265**, $R^2 = Et$) in polyphosphoric acid at 200–230°C for 10 min gave 1-substituted 7-alkyl-1,4-dihydro-1,8-naphthyridine-3-carboxylic acids (**1022**, $R = Me, Et$; $R^1 = alkyl$; $R^2 = H$) in 17–56% yields (71GEP2108046). From the mother liquor, 2-(substituted amino)-6-alkylpyridines could be recovered.

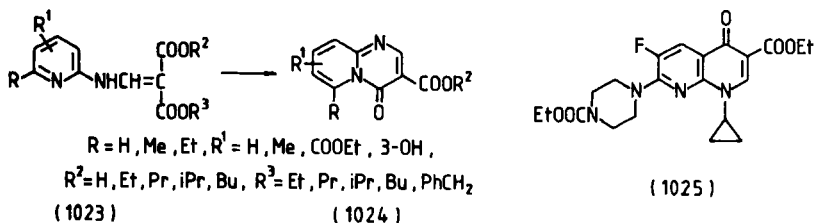


The ring closure of *N*-ethyl-*N*-[6-(4-methyl-1-piperidyl)-2-pyridyl]aminomethylenemalonate (**265**, $R = 4\text{-methyl-1-piperidyl}$, $R^1 = R^2 = Et$) by heating in polyphosphoric acid at 140°C for 15 min afforded ethyl 1-ethyl-1,8-naphthyridine-3-carboxylate (**1022**, $R = 4\text{-methyl-1-piperidyl}$, $R^1 = R^2 = Et$) in 78% yield (74GEP2362553).

7-Methyl-1-(2,2,2-Trifluoroethyl)-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid (**1022**, $R = Me$; $R^1 = CF_3CH_2$; $R^2 = H$) was obtained in 16% yield by the cyclization of diethyl *N*-(2,2,2-trifluoroethyl)-*N*-(6-methyl-2-pyridyl)aminomethylenemalonate (**265**, $R = Me$; $R^1 = CF_3CH_2$, $R^2 = Et$) in polyphosphoric acid at 200–220°C for 10 min [77JAP-(K)139094].

The ring closure of 2-pyridylaminomethylenemalonates (**1023**, both 6-substituted and 6-unsubstituted) took place readily in phosphoryl chloride in the presence of a catalytic amount of polyphosphoric acid ($\sim 1\text{--}10\%$) at reflux temperature. When hydrogen chloride gas evolution ceased, the reaction mixtures were treated with the appropriate alcohol, and hydrochloride salts of pyrido[1,2-*a*]pyrimidine-3-carboxylates (**1024**) were ob-

tained in high yields (72AF815, 72MIP1, 72MIP2; 79BEP873195; 84S152). Cyclization did not proceed in phosphoryl chloride alone (72AF815; 84S152). The cyclization was also unsuccessful if the pyridine moiety contained a bromo, hydroxy, or acetamido substituent in position 6 (**1023**, $R = \text{Br, OH, NHAc}$), and in the case of dimethyl *N*-(6-methyl-2-pyridyl)aminomethylenemalonate (**1023**, $R = R^2 = R^3 = \text{Me}$, $R^1 = \text{H}$) (72AF-815; 84S152).



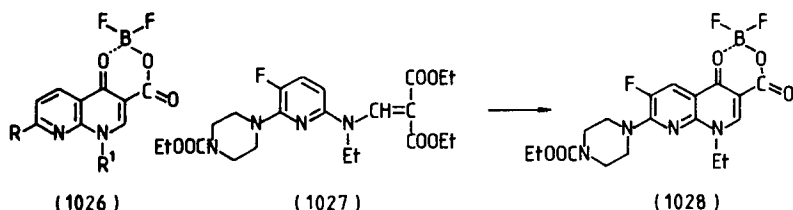
The ring closure of diethyl *N*-(6-methyl-2-pyridyl)aminomethylenemalonate (**1001**, $R = \text{Me}$, $R^1 = \text{H}$) was carried out on a large scale in chlorobenzene on the action of a mixture of phosphoryl chloride and polyphosphoric acid at 125–130°C for 10–12 hr to give the hydrochloride of pyrido[1,2-*a*]pyrimidine-3-carboxylate (**1002**, $R = \text{Me}$, $R^1 = \text{H}$) in good yield after treatment of the reaction mixture with ethanol (77MIP1).

The cyclization of *N*-(6-methyl-2-pyridyl)aminomethylenemalonate (**1001**, $R = \text{Me}$, $R^1 = \text{H}$), labeled on one of the carboxyl groups with ^{14}C , gave labeled 1,8-naphthyridine (**1003**, $R = \text{Me}$, $R^1 = \text{H}$) in boiling diphenyl ether and labeled pyrido[1,2-*a*]pyrimidine (**1002**, $R = \text{Me}$, $R^1 = \text{H}$) in a mixture of phosphoryl chloride and polyphosphoric acid in 77% and 85% yields, respectively (73MI2; 75MI2).

It was claimed that the cyclization of 2-pyridylaminomethylenemalonates (**1023**, $R = \text{H, Me}$, $R^1 = \text{H, 4-Me}$) in a 2 : 1 mixture of acetic acid and concentrated sulfuric acid afforded pyrido[1,2-*a*]pyrimidine-3-carboxylic acids (**1024**, $R = \text{H, Me}$, $R^1 = \text{H, 8-Me}$, $R^2 = \text{H}$), but only the melting points of the esters ($R^2 = \text{Et}$) were given (74MIP2) as evidence.

1-Cyclopropyl-1,4-dihydro-1,8-naphthyridine-3-carboxylate (**1025**) was prepared in 43–48% yields by the cyclization of *N*-cyclopropyl-*N*-[6-(4-ethoxycarbonyl-1-piperazinyl)-5-fluoro-2-pyridyl]aminomethylene-malonate (**111**) in acetic acid by the action of concentrated sulfuric acid at 55–60°C for 1 hr (85EUP153163, 85EUP153828, 85EUP159174; 86EUP172651; 88EUP265230).

The cyclization of diethyl *N*-alkyl-*N*-(6-alkyl-2-pyridyl)aminomethylenemalonates (**265**, R and $R^1 = \text{alkyl}$, $R^2 = \text{Et}$) could be carried out easily in diphenyl ether or in Dowtherm A in the presence of a boron trifluoride



etherate complex at 225–242°C for a few minutes. Depending on the work-up, 1,8-naphthyridine-3-carboxylic acid-BF₂ chelate (**1026**) or 1,8-naphthyridine-3-carboxylic acids (**1022**, R = Me, Et; R¹ = Me, Et; Pr; R² = H) were obtained in 59–94% yields (79GEP2855279). For example, when a mixture of 2-pyridylaminomethylenemalonate (**265**, R = Me, R¹ = R² = Et) and boron trifluoride THF complex in Dowtherm A was added dropwise to Dowtherm A at 230°C over 32 min, the mixture was stirred for 5 min, the low-boiling substances were distilled out and cooled to ambient temperature, then a 94% yield of chelate (**1026**, R = Me, R¹ = Et) could be obtained. As ether, THF, dibutyl ether, or diethyl ether was applied as boron trifluoride etherate.

Diethyl N-ethyl-N-[6-(4-ethoxycarbonyl-1-piperazinyl)-5-fluoro-2-pyridyl]aminomethylenemalonate (**1027**) was cyclized on the action of boron trifluoride etherate complex in diphenyl ether at 228–231°C for 30 min to give the 1,8-naphthyridine derivative (**1028**) in 90% yield [84JAP(K)80683].

b. Cyclization of Further Six-Membered N-(α -N-Heterocyclic)aminomethylenemalonates

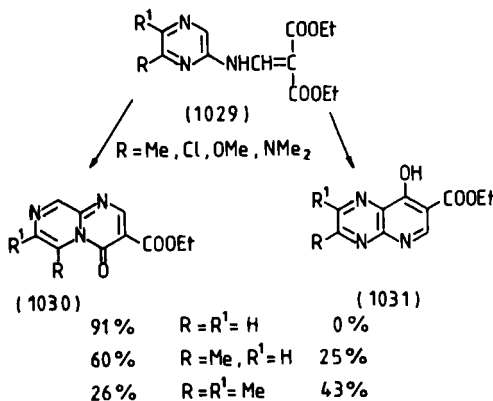
2-Pyrazinylaminomethylenemalonate (**1029**, R = R¹ = H) was heated in Dowtherm A at 255°C for 10 min to give pyrazino[1,2-*a*]pyrimidine-3-carboxylate (**1030**, R = R¹ = H) in 89% yield (68JMC1045).

The ring closure of the 6-methoxy derivative (**1029**, R = OMe, R¹ = H) under similar conditions afforded pyrido[2,3-*b*]pyrazine (**1031**, R = OMe, R¹ = H) in 78% yield (72CB3118).

The cyclization of N-(6-substituted 2-pyrazinyl)aminomethylenemalonates (**1029**, R \neq H) in diphenyl ether at 250–270°C for 5–30 min gave pyrido[2,3-*b*]pyrazines (**1031**, R \neq H) in 10–85% yields [73JAP(K)23798; 74CPB1864, 74JAP(K)56996]. In addition to 10% of pyrido[2,3-*b*]pyrazine (**1031**, R = Me, R¹ = H), Nakao *et al.* isolated 20% of isomeric nitrogen bridgehead bicycle (**1030**, R = Me, R¹ = H) from the reaction mixture of the 6-methylpyrazine derivative (**1029**, R = Me, R¹ = H) (74CPB1864).

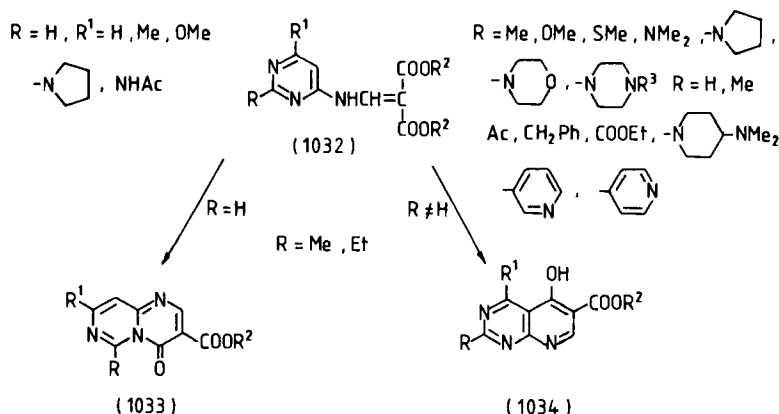
They failed to cyclize the 6-chloro derivative. Only tar formation was observed.

Later, Tanaka *et al.* successfully cyclized *N*-(6-chloro-2-pyrazinyl)aminomethylenemalonate (**1029**, R = Cl, R¹ = H) to pyrido[2,3-*b*]pyrazine-carboxylate (**1031**, R = Cl, R¹ = H) in 35% yield by heating in diphenyl ether at 260–270°C [75JAP(K)53394, 75YZ1092]. Tanaka and Narita obtained pyrazino[1,2-*a*]pyrimidine (**1030**, R = R¹ = H) from **1029** (R = R¹ = H), whereas mixtures of pyrazino[1,2-*a*]pyrimidines (**1030**, R = Me, R¹ = H, Me) and pyrido[2,3-*b*]pyrazines (**1031**, R = Me, R¹ = H, Me) were produced from the 6-methyl derivative of 2-pyraziny-laminomethylenemalonate (**1029**, R = Me, R¹ = H, Me) in boiling Dowtherm A for 20 min (75YZ1092).



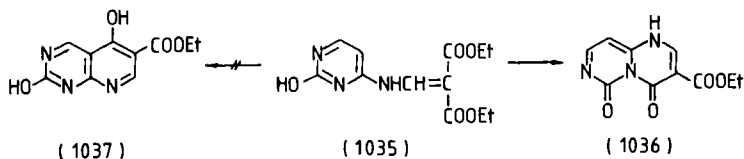
The cyclization of diethyl 2-pyrimidinylaminomethylenemalonate in boiling trichlorobenzene gave pyrimido[1,2-*a*]pyrimidine-3-carboxylate in 19% yield (72JMC1203). The diethyl *N*-(4,6-dimethyl 2-pyrimidinylamino)-methylenemalonate could not be cyclized by heating in trichlorobenzene (72JMC1203).

The thermal ring closure of *N*-(2-substituted 4-pyrimidyl)aminomethylenemalonates (**1032**, R ≠ H) by heating in mineral oil at 320°C (67USP3320257), in diethyl phthalate at 285°C (67USP3320257), in boiling Dowtherm A (70CPB1385; 72JOC3980; 76GEP2544369, 76USP3992380; 78BRP1514575; 82JHC1581), or in refluxing diphenyl ether (68JAP6227; 71CPB1426, 71CPB1482; 72JOC3980; 74GEP2341146; 77GEP2729661; 79GEP2856527) generally afforded pyrido[2,3-*d*]pyrimidine-6-carboxylates (**1034**, R ≠ H) in 11–97% yields. Thermal ring closure of *N*-(2-unsubstituted 4-pyrimidyl)aminomethylenemalonates (**1032**, R = H) in boiling Dowtherm A (80CPB2148) or diphenyl ether at 205–210°C gave pyrim-



ido[1,6-*a*]pyrimidine-3-carboxylates (**1033**, $R = H$) in 69–82% yields (72JOC3980).

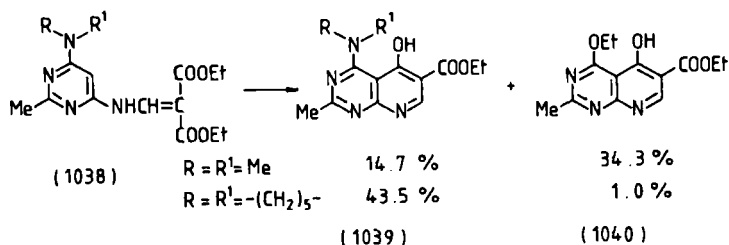
In contrast with an earlier statement (72USP3673184), it was proved by 1H -NMR investigations (82JHC1581) that the cyclization of *N*-(2-hydroxy-4-pyrimidyl)aminomethylenemalonate (**1035**) by heating in boiling Dowtherm A for 10 min occurred at the nitrogen atom, and not the carbon atom, to give 5,8-dihydro-4,6-dioxo-4*H*-pyrido[1,6-*a*]pyrimidine-3-carboxylate (**1036**) in 61% yield. Later, it was again claimed that the cyclization product in the previous reaction was pyrido[2,3-*b*]pyrimidine (**1037**) [87MIP6; 88JAP(K)183582].



Pyrido[2,3-*d*]pyrimidine-6-carboxylates (**1034**, $R = Me$, $R^1 = NHPh$, $NHPh-4Cl$) were prepared in 92–99% yields from 4-amino-6-arylaminomethylpyrimidines and EMME in one-pot reactions in Dowtherm A at 250°C for 40 min (70CPB1385).

When *N*-[6-(disubstituted amino)-4-pyrimidinyl]aminomethylenemalonates (**1038**) were cyclized by heating in Dowtherm A at 250°C for 15 min, both 4-(disubstituted amino)pyrido[2,3-*d*]pyrimidine-6-carboxylates (**1039**) and the 4-ethoxy derivative (**1040**) were prepared (70CPB1385).

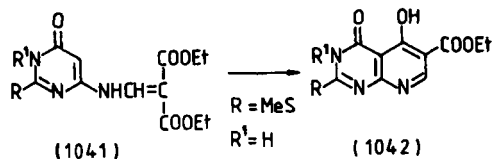
Unsuccessful attempts were made to cyclize *N*-(6-amino-4-pyrimi-



dinyl)aminomethylenemalonates (**1032**, $\text{R} = \text{H}$, Me , $\text{R}^1 = \text{NH}_2$) to the corresponding bicyclics (**1033**, $\text{R} = \text{H}$, $\text{R}^1 = \text{NH}_2$, and **1034**, $\text{R} = \text{Me}$, $\text{R}^1 = \text{NH}_2$) (70CPB1385; 72JOC3980) under a variety of conditions, but the 6-acetamido derivatives (**1032**, $\text{R} = \text{H}$, SMe ; $\text{R}^1 = \text{NHAc}$) afforded pyrimido[1,6-*a*]pyrimidine-3-carboxylate (**1033**, $\text{R} = \text{H}$, $\text{R}^1 = \text{NHAc}$) or pyrido[2,3-*d*]pyrimidine-6-carboxylate (**1034**, $\text{R} = \text{MeS}$, $\text{R}^1 = \text{NHAc}$) in 70% yield when heated in diphenyl ether or Dowtherm A, respectively (72JOC3980).

Although the thermal cyclization of *N*-(6-oxo-4-pyrimidinyl)aminomethylenemalonate (**1041**, $\text{R} = \text{R}^1 = \text{H}$) was unsuccessful when it was heated in boiling Dowtherm A for 20 min, the 2-methylthio derivative (**1041**, $\text{R} = \text{MeS}$, $\text{R}^1 = \text{H}$) gave pyrido[2,3-*d*]pyrimidine-6-carboxylate (**1042**, $\text{R} = \text{MeS}$, $\text{R}^1 = \text{H}$) in 73% yield (72JOC3980).

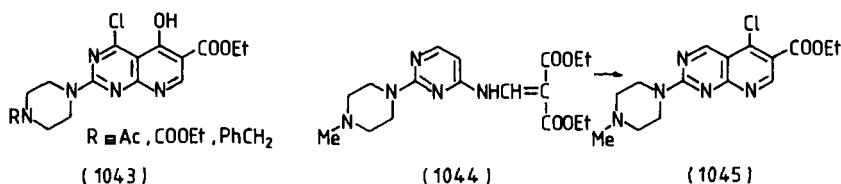
The cyclization of *N*-(2-alkoxy-4-pyrimidinyl)aminomethylenemalonates (**1041**, $\text{R} = \text{MeO}$, EtO , $\text{R}^1 = \text{Me}$) in boiling diphenyl ether for 1 hr gave pyrido[2,3-*d*]pyrimidine-6-carboxylates (**1042**, $\text{R} = \text{MeO}$, EtO ; $\text{R}^1 = \text{Me}$ in 60–70% yields (89JHC1089).



Matsumoto *et al.* unsuccessfully tried to isomerize pyrimido[1,6-*a*]pyrimidine-6-carboxylate (**1033**, $\text{R} = \text{H}$, $\text{R}^1 = \text{H}$, Me , pyrrolidine) thermally to the corresponding pyrido[2,3-*d*]pyrimidine-3-carboxylate (**1034**, $\text{R} = \text{H}$) (80CPB2148).

Pyrimido[2,3-*d*]pyrimidine-6-carboxylates (**1043**) were prepared in 28–85% yields on the cyclization of 4-pyrimidinylaminomethylenemalonates (**54**) by heating in boiling 1,2,4-trichloro- or 1,2-dichlorobenzene [87JAP(K)142177].

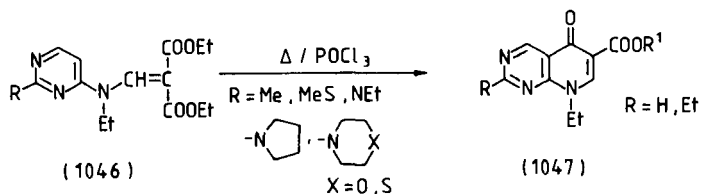
N-2-(4-Methyl-1-piperazinyl)-4-pyrimidinylaminomethylenemalonate (**1044**) was heated in phosphoryl chloride at 95°C for 5 hr to give 5-chloropyrido[2,3-*d*]pyrimidine-6-carboxylate (**1045**) in 85% yield (74GEP2341146).



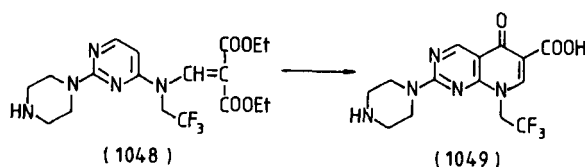
Depending on the work-up, pyrido[2,3-*d*]pyrimidine-6-carboxylates (**1047**, R¹ = Et) or 6-carboxylic acids (**1047**, R¹ = H) were prepared in high yields on the heating of *N*-ethyl-*N*-(4-pyrimidinyl)aminomethylenemalonates (**1046**) in phosphoryl chloride for 6 hr [73JAP(K)91093].

Pipemidic acid was prepared in 54% yield by the cyclization of *N*-ethyl-*N*-(4-pyrimidinyl)aminomethylenemalonate (**1046**, R = pyrrolidino) on heating in polyphosphoric acid at 200–230°C for 10 min [73JAP(K)8800].

The cyclization of the 2-(4-methylpiperazinyl) derivative of **1046** (R = 4-methyl-1-piperazinyl) afforded pyrimido[2,3-*d*]pyrimidine-6-carboxylate (**1047**, R = 4-methyl-1-piperazinyl, R¹ = Et) in 82% yield when it was heated in polyphosphoric acid at 140°C for 20 min (74GEP2341146).

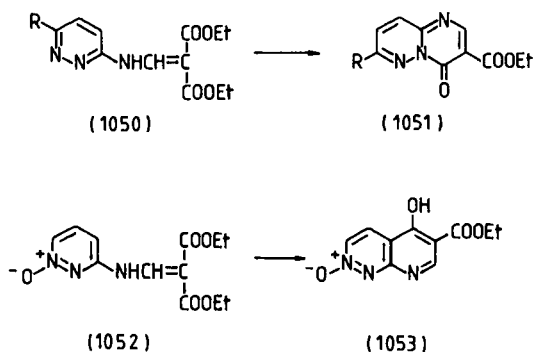


The ring closure of *N*-(2,2,2-trifluoroethyl)-*N*-[2-(1-piperazinyl)-4-pyrimidinyl]aminomethylenemalonate (**1048**) in polyphosphoric acid at 200–220°C for 10 min yielded 8-trifluoroethylpyrido[2,3-*d*]pyrimidine-6-carboxylic acid (**1049**) [77JAP(K)139094].

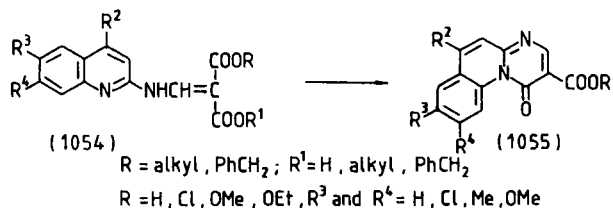


The thermal ring closure of 3-pyridazinylaminomethylenemalonate (**1050**, R = H) by heating in boiling diphenyl ether afforded pyrimido[1,2-*b*]pyridazine-3-carboxylate (**1051**, R = H) in 73% yield (68TL33). Efforts to cyclize the 6-chloro derivative (**1050**, R = Cl) under similar conditions were unsuccessful (68TL33), but when 3-amino-6-chloropyridazine was reacted with EMME in boiling diphenyl ether (78GEP2814777; 80USP4231928) or in polyphosphoric acid at 120°C for 2 hr (85H1), 7-chloropyrimido[1,2-*b*]pyridazine-3-carboxylate (**1051**, R = Cl) was prepared in 56% and 67% yields, respectively.

The thermal cyclization of 3-pyridazinylaminomethylenemalonate *N*-oxide (**1052**) by heating in diphenyl ether at 250°C for 15 min gave pyrido[2,3-*c*]pyridazine-6-carboxylate *N*-oxide (**1053**) in 70% yield (72JHC351).

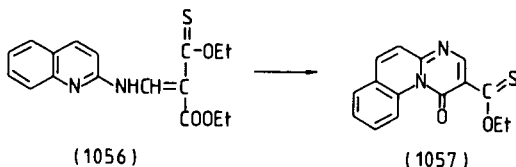


2-Quinolinylaminomethylenemalonates (**1054**) were cyclized to the angular pyrimido[1,2-*a*]quinoline-2-carboxylates (**1055**) in moderate or good yields by heating in boiling diphenyl ether (72JMC1203) or in Dowtherm A (74MIP1; 75GEP2513930; 77GEP2628751, 77GEP2630469, 77USP4031217; 78GEP2801248, 78YZ1279; 79USP4175193) at 230–255°C for 60–120 min. They were also cyclized by the action of polyphosphoric acid in boiling phosphoryl chloride for 3–7 hr (74MIP1; 79MIP1). Under



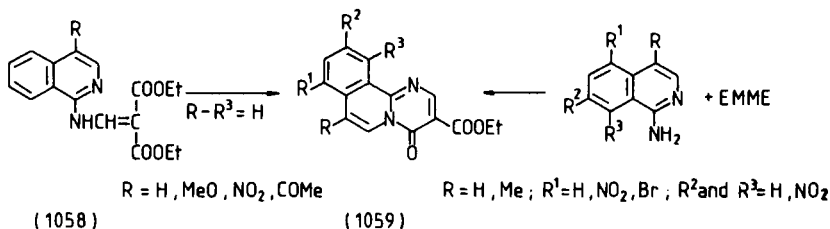
the latter conditions, a shorter reaction period was possible when the half ester (**1054**, $R = \text{Et}$, $R^1 = \text{H}$) was applied (74MIP1). Dimethyl 2-quinolinylinomethylenemalonate (**1054**, $R = R^1 = \text{Me}$) could be cyclized only thermally (84S152).

The cyclization of *O,O*-diethyl 2-quinolinylinomethylenethionmalonate (**1056**) by heating in a mixture of polyphosphoric acid and phosphoryl chloride afforded 55–60% of 1-oxypyrimido[1,2-*a*]quinoline-2-carboxylate (**1055**, $R = \text{Et}$, $R^2-R^4 = \text{H}$), while heating in Dowtherm A at 250°C led to 1-oxypyrimido[1,2-*a*]quinoline-2-thiocarboxylate (**1057**) in 15–17% yields (74MIP1; 84S152).



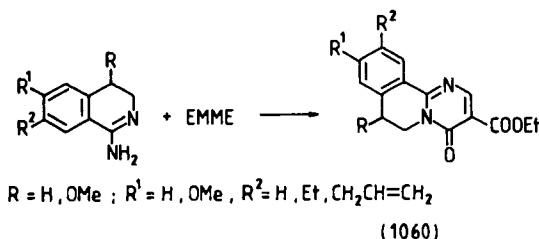
Pyrimido[1,2-*a*]quinoline-2-carboxylate (**1055**, $R = \text{Et}$, $R^2-R^4 = \text{H}$) was obtained in 50% yield when 2-aminoquinoline was reacted with EMME in boiling Dowtherm A for 20 min (74MIP1). The 6-hydroxy derivative of **1055** ($R = \text{Et}$, $R^2 = \text{OH}$, $R^3 = R^4 = \text{H}$) was prepared in 20% yield when 2-amino-4-hydroxyquinoline and EMME were heated at 170°C for 8 hr (71IJC201). The angular pyrimido[1,2-*a*]quinoline-2-carboxylate (**1055**, $R = \text{Et}$, $R^2-R^4 = \text{H}$) could not be transformed into the linear isomer [77JCS(P1)780].

The thermal ring closure of 1-isoquinolinylinomethylenemalonates (**1058**) by heating in diphenyl ether at 235–260°C for 5–15 min gave pyrimido[2,1-*a*]isoquinoline-3-carboxylates (**1059**) in 67–83% yields [78USP-4127720; 84JAP(K)172472].

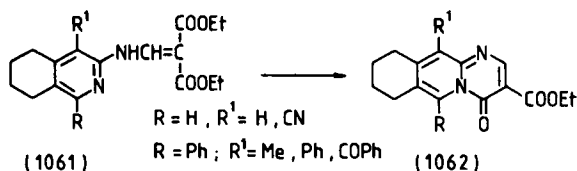


The reaction of 1-aminoisoquinolines and EMME by heating in boiling DMF for 18 hr yielded pyrimido[2,1-*a*]isoquinoline-3-carboxylates (**1059**) (85EUP143001).

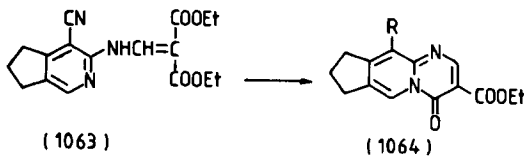
When the temperature of the reaction mixture of 1-amino-3,4-dihydroisoquinolines and EMME in toluene was gradually increased to boiling, and the reaction mixture was then refluxed for 5 min, 6,7-dihydropyrimido[2,1-*a*]isoquinoline-3-carboxylates were formed (**1060**) in 79–83% yields (78USP4127720).



N-(6,7,8,9-Tetrahydro-3-isoquinoliny)aminomethylenemalonates (**1061**) were cyclized by heating in diphenyl ether at 180°C for 3 hr (83KGS1279), or at 250°C for 1 hr (84KFZ931), or on the action of polyphosphate (88MI9) to give pyrimido[1,2-*b*]isoquinoline-3-carboxylates (**1062**) in 75–90% yields.

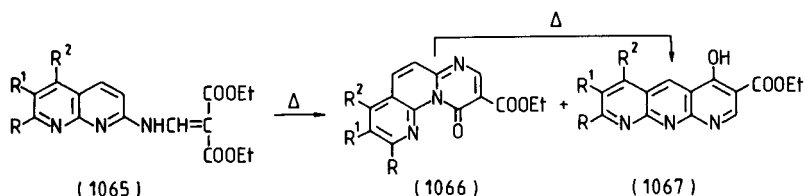


Cyclopenta[*c*]pyridylaminomethylenemalonate (**1063**) was cyclized by the action of a mixture of acetic anhydride and concentrated sulfuric acid at 90°C for 1 hr to give the tricyclic nitrogen bridgehead ring system (**1064**, $R = CN$) in 60% yield (83KGS1279).



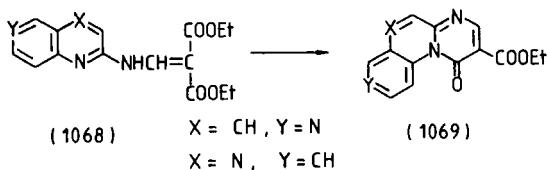
The reaction of 3-aminocyclopenta[*c*]pyridine and EMME at 150°C for 2 hr afforded cyclopenta[*g*]pyrido[1,2-*a*]pyrimidine-3-carboxylate (**1064**, $R = H$) in 54% yield (84KFZ931).

Depending on the reaction period, the thermal cyclization of *N*-(1,8-naphthyridine-2-yl)aminomethylenemalonates (**1065**) by heating in Dowtherm A gave the angular pyrimido[1,2-*a*][1,8]naphthyridinecarboxylates (**1066**), or the linear anthyridines (**1067**), or a mixture of these tricycles [67G1274; 69G677; 71G129, 71JCS(C)2985]. Pyrimido[1,2-*a*][1,8]naphthyridinecarboxylates (**1066**) were isomerized to anthyridines (**1067**) when heated in vaseline oil at 300°C for 5 min (69G677) or in boiling Dowtherm A [77JCS(P1)789].

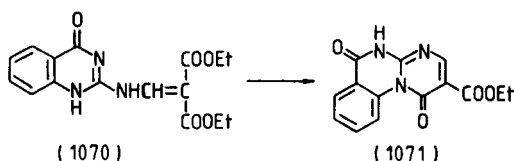


Pyrimido[1,2-*a*][1,6]naphthyridinecarboxylate (**1069**, X = CH, Y = N) was obtained in 55% yield on the cyclization of *N*-(1,6-naphthyridin-2-yl)aminomethylenemalonate (**1068**, X = CH, Y = N) by heating in Dowtherm A for 10 min (74JHC151).

The thermal ring closure of 2-quinoxyalylaminomethylenemalonate (**1068**, X = N, Y = CH) by heating in Dowtherm A at 250–255°C for 1 hr gave pyrimido[1,2-*a*]quinoxalinecarboxylate (**1069**, X = N, Y = CH) in 82% yield [77JCS(P1)789]. Further heating did not result in formation of the isomeric linear tricycle.

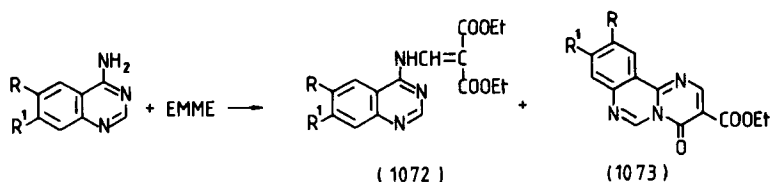


The cyclization of *N*-(4-oxoquinazolin-2-yl)aminomethylenemalonate (**1070**) by heating in diphenyl ether at 240°C for 10 min occurred at position 1 to afford the angular ring system (**1071**) in 81% yield (89JHC161). Cycliza-

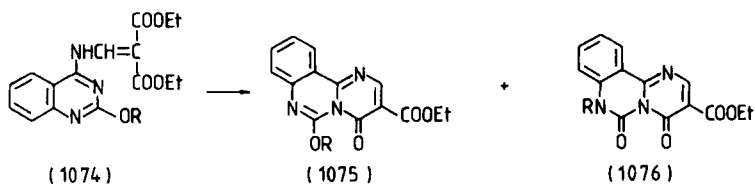


tion in paraffin gave a lower yield, and the tricyclic product (**1071**) was impure.

4-Aminoquinazolines (R and $R^1 = H, Cl$) were reacted with EMME at $150^\circ C$ for 2 hr to give a mixture of 4-quinazolinylaminomethylenemalonates (**1072**) and pyrimido[1,2-*c*]quinazolinecarboxylates (**1073**) (81EUP30156).



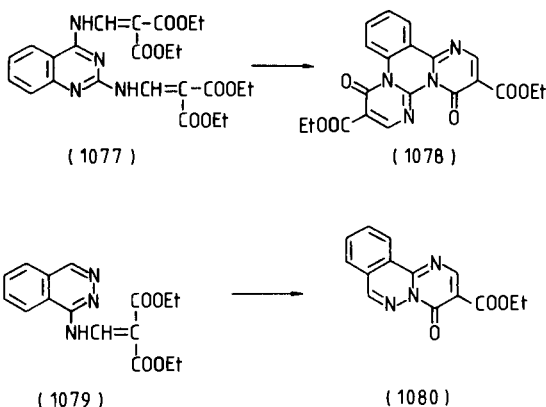
The reaction of 4-amino-6,7-dimethylquinazoline and EMME in DMF at $110^\circ C$ for 4 hr gave pyrimido[1,2-*c*]quinazolinecarboxylate (**1073**, $R = R^1 = Me$) in 19% yield (81EUP30156), while that of the 4-aminoquinazoline derivative [$R = EtCH(Me)CH(Me)CONH-$, $R^1 = H$] and EMME in diphenyl ether at $250^\circ C$ for 40 min afforded the tricyclic derivative (**1073**, $R = EtCH(Me)CH(Me)CONH-$, $R^1 = H$) in 86% yield [86JAP(K)50983]. 4-Quinazolinylaminomethylenemalonates (**1072**) were cyclized by heating in diphenyl ether at 250 – $260^\circ C$ for 20 min to give pyrimido[1,2-*c*]quinazolinecarboxylates (**1073**) (81EUP30156). Following the cyclization of *N*-(2-alkoxy-4-quinazolinyl)aminomethylenemalonates (**1074**) in diphenyl ether at $260^\circ C$ for 15–32 min, a roughly 1 : 1 mixture of 6-alkoxy and 7-alkyl-6-oxopyrimido[1,2-*c*]quinazoline-3-carboxylates (**1075** and **1076**) was isolated (81EUP30156).



Bis(aminomethylenemalonate) (**1077**) was cyclized in diphenyl ether at $260^\circ C$ for 35 min to afford dipyrimido[1,2-*a*:1',2'-*c*]quinazoline-3,8-dicarboxylate (**1078**) in 50% yield (81EUP30156).

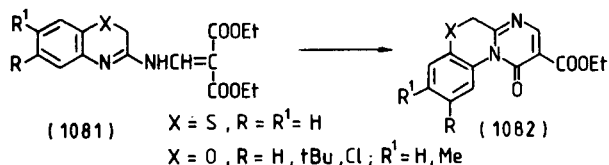
The ring closure of 1-phthalazinylaminomethylenemalonate (**1079**) in boiling propanol yielded pyrimido[2,1-*a*]phthalazinecarboxylate (**1080**) [74CR(C)209].

5*H*-Pyrimido[2,1-*c*][1,4]benzoxazinecarboxylates (**1082**, $X = O$) and



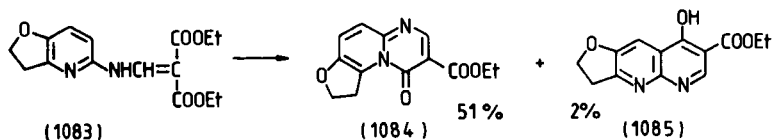
5*H*-pyrimido[2,1-*c*]-1,4-benzothiazinecarboxylates (**1082**, *X* = S) were obtained on the cyclization of *N*-(2*H*-1,4-benzoxazin-3-yl)- and *N*-(2*H*-1,4-benzothiazin-3-yl)aminomethylenemalonates (**1081**, *X* = O, S) on the action of sodium ethylate in ethanol at 20°C for 2 hr (81USP4254118).

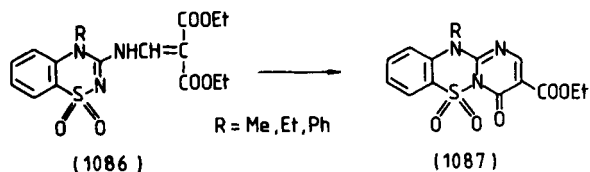
N-(2*H*-1,4-Benzoxazin-3-yl)aminomethylenemalonate (**1081**, *X* = O; *R* = H, *R*¹ = COOEt) was cyclized by heating in polyphosphoric acid at 100°C for 1 hr to give 5*H*-pyrimido[2,1-*c*]-1,4-benzothiazinedicarboxylate (**1082**, *R* = H, *R*¹ = COOEt) in 65% yield (81USP4254118).



The cyclization of *N*-(furo[3,2-*b*]pyridin-5-yl)aminomethylenemalonate (**1083**) by heating in boiling Dowtherm A for 15 min afforded a mixture of the angular and linear isomeric tricycles (**1084** and **1085**) (84CPB4914).

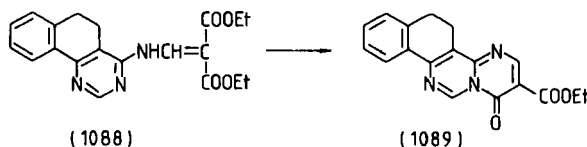
The thermal ring closure of *N*-(4*H*-1,2,4-benzothiadiazine 1,1-dioxide-3-yl)aminomethylenemalonates (**1086**) in Dowtherm A at 200°C for 8 hr



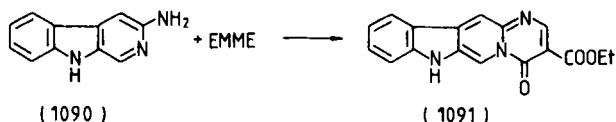


afforded pyrimido[1,2-*b*][1,2,4]benzothiazine-3-carboxylate 6,6-dioxides (**1087**) in 70–75% yields (89JHC473).

The thermal cyclization of *N*-[4-benzo[*h*]quinazolin-4-yl]aminomethylenemalonate (**1088**) in Dowtherm A at 250–255°C for 12 hr gave benzo-(*h*)pyrimido[1,2-*c*]quinazoline-2-carboxylate (**1089**) in 75% yield (86-H1119).

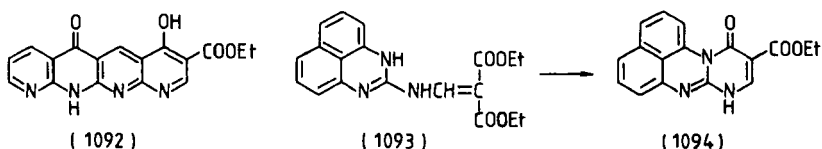


The cyclocondensation of 3-aminopyrido[3,4-*b*]indole (**1090**) and EMME in boiling acetic acid and propionic acid for 8 hr or 4 hr gave pyrimido[2', 1' : 6, 1]pyrido[3,4-*b*]indolecarboxylate (**1091**) in 52% and 65% yields, respectively [87MIP4, 87MIP5; 88IJC(B)484].



The ring closure of 2-anthryridinylaminomethylenemalonate (**98**) by heating in boiling Dowtherm A for 2 hr gave 1,10,11,12-tetrazanaphthacene-3-carboxylate (**1092**) in 73% yield. The tetracycle (**1092**) was prepared in 88% yield when 2-aminoanthryridin-5(10*H*)-one was reacted with EMME under the previous conditions (74FES366).

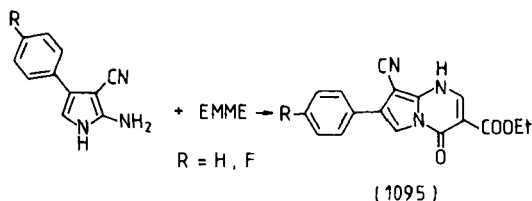
11-Oxopyrimido[1,2-*a*]perimidine-10-carboxylate (**1094**) was obtained in



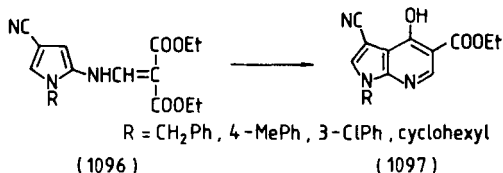
98% yield by the thermal cyclization of 2-perimidiny laminomethylenemalonate (**1093**) in boiling diphenyl ether for 10 min (89AP303).

c. Cyclization of Other *N*-(α -*N*-Heterocyclic)-aminomethylenemalonates

Pyrrolo[1,2-*a*]pyrimidine-3-carboxylates (**1095**) were prepared in 76% yields by the cyclization of 2-pyrrolylaminomethylenemalonates (**60**, R = H, F) in boiling Dowtherm A for 2 min under argon, or in 68–74% yields in DMF at ambient temperature on the action of potassium *tert*-butoxide for 18–24 hr (87JHC297), or in 70% yield in boiling DMF for 1 hr (87FES787), and in 68–70% yields by the cyclocondensation of 2-aminopyrroles and EMME in boiling ethanol for 30–36 hr (87JHC297) or in 60% yield by heating in the melt at 210–220°C for 40 min (87FES787).

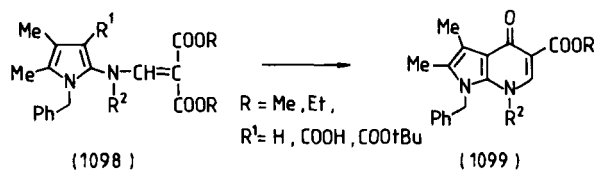


If the nitrogen atom of the pyrrole ring was substituted, then pyrrolo[2,3-*b*]pyridinecarboxylates (**1097**) were obtained in 68–74% yields on the thermal cyclization of *N*-(1-substituted 2-pyrrolyl)aminomethylenemalonates (**1096**) by heating in diphenyl ether at 250°C for 20 min [75JCS(P1)1910; 89JHC1029].



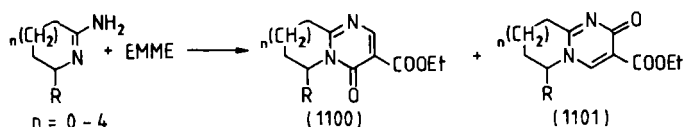
1-Benzylpyrrolo[2,3-*b*]pyridine-5-carboxylates (**1099**, R² = H) were prepared in 54–84% yields by the cyclization of *N*-(1-benzyl-2-pyrrolyl)aminomethylenemalonates (**1098**, R² = H) in boiling Dowtherm A for 8–15 min or in 49–73% yields on the action of polyphosphate at 90–125°C for 1.0–3.5 hr (85JHC1429).

N-Methyl-*N*-(1-benzyl-2-pyrrolyl)aminomethylenemalonate (**1098**, R =



R² = Me, R¹ = COOH) was cyclized by heating in polyphosphate at 100°C for 25 hr to afford 1-benzyl-7-methylpyrrolo[2,3-*b*]pyridine-5-carboxylate (**1099**, R = R² = Me) in 15% yield (85JHC1429).

The reaction of semicyclic amidines and EMME afforded a mixture of isomeric pyrimidin-4-ones (**1100**), (**1101**) (80BEP-883216, 80GEP3017625; 82JHC909, 82MI4).



A detailed study of the reaction of semicyclic amidines and EMME revealed that the yields of isomeric pyrimidin-4-ones (**1100**) increased with increasing ring size (*n*) of the amidines when the ethanolic solution of the amidine was added dropwise to the ethanolic solution of EMME at -10°C (see Table VIII) (82JHC909, 82MI4).

TABLE VIII
YIELDS OF ISOMERIC BICYCLIC PYRIMIDIN-4-ONE (**1100**) AND
PYRIMIDIN-2-ONE (**1101**), FORMED IN THE REACTION OF EMME
AND SEMICYCLIC AMIDINE

| <i>n</i> | R | (1100) Yield % | (1101) Yield % | References |
|----------|----|----------------------------|----------------------------|-------------|
| 0 | H | 69.7 | 16.0 | 82JHC909 |
| 0 | Me | 65.0 | 32.0 | 82JHC909 |
| 1 | H | 72.0 | 25.0 | 82JHC909 |
| 1 | Me | 84.0 | 0.0 | 82JHC909 |
| 2 | H | 80.5 | 8.9 | 82JHC909 |
| 2 | Me | 56.0 | 0.0 | 82JHC909 |
| 3 | H | 80.0 | 4.8 | 82JHC909 |
| 4 | H | 41.5 | In trace | Unpublished |

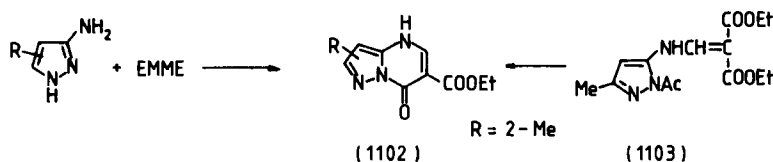
In the case of 2-aminopyrroline ($n = 0$, $R = H$), when EMME was added dropwise to the solution of amidine, 23% of 4-oxo isomer (**1100**, $n = 0$; $R = H$), and 72% of 2-oxo isomer (**1101**, $n = 0$; $R = H$) were obtained (82JHC909, 82MI4). The presence of a methyl substituent ($R = Me$) influenced the ratio of **1100** and **1101** ($R = Me$): in the five-membered series, it caused a higher yield of 2-oxoisomer (**1101**, $R = Me$), probably by enhancing the nucleophilic power of the ring nitrogen in the first step of the reaction. From higher homologous amidines ($n = 1, 2$; $R = Me$), however, only 4-oxo derivatives (**1100**, $n = 1, 2$; $R = Me$) were formed, and 2-oxo isomers (**1101**, $n = 1, 2$; $R = Me$) could not even be detected by TLC (82JHC909, 82MI4).

Bicyclic pyrimidin-4-ones (**1100**, $R = H$, $n = 0-3$; $R = Me$, $n = 1$) were also prepared from the appropriate lactim ether and EMME in the presence of ammonia or ammonium acetate [73JAP(K)34897; 75MIP1]. Pyrimido[1,2-*a*]azepine-3-carboxylates (**1100**, $R = H$, Ph; $n = 2$) were prepared in the reaction of 7-aminotetrahydro-2*H*-azepines ($R = H$, Ph; $n = 2$) and EMME or in the reaction of *O*-methylcaprolactim and diethyl aminomethylenemalonate in ethanol [73JAP(K)34897; 75MIP1].

The reaction of ^{15}N -labeled amidines ($n = 0$ and 2) and EMME yielded condensed 4-oxopyrimidine-3-carboxylates (**1100**, $n = 0$ and 2) ^{15}N -labeled at position 1 [85JCS(P2)1881].

The reaction of 3-aminopyrazole and EMME in the melt at 100°C for 30 min gave a mixture of ethyl pyrazolo[1,5-*a*]pyrimidine-6-carboxylate (**64**) and diethyl 3-pyrazolylaminomethylenemalonate in 10% and 25% yields, respectively (70CB3252). The heating of diethyl 3-pyrazolylaminomethylenemalonate in boiling xylene or in boiling acetic acid for 3–6 hr gave pyrazolo[1,5-*a*]pyrimidine-6-carboxylate (**64**) in 24% and 95% yields, respectively (70CB3252).

The cyclocondensation of 3-aminopyrazoles and EMME in boiling acetic acid afforded pyrazolo[1,5-*a*]pyrimidine-6-carboxylates (**64** and **1102**) in good yields [59JOC779; 62CPB620; 70CB3252; 73GEP2257547; 75MC312; 77GEP2648770, 77IJC(B)349, 77USP4021556; 82JMC235; 85JHC601]. Pyrazolo[1,5-*a*]pyrimidine-6-carboxylate (**64**) was also prepared in the reaction of 3-aminopyrazole and EMME by heating in the melt at 110°C for 1 hr (712IJC201).

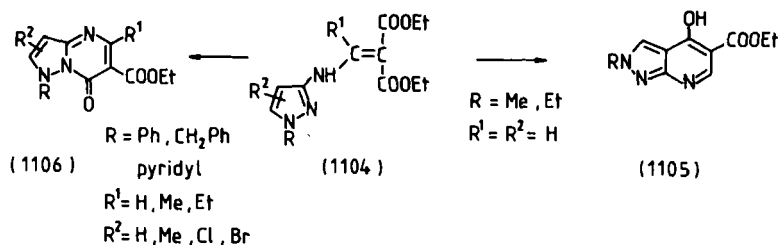


The cyclization of diethyl *N*-(5-phenyl-3-pyrazolyl)aminomethylenemalonate by heating in the melt at 180°C gave 2-phenylpyrazolo[1,5-*a*]pyrimidine-6-carboxylate (**1102**, R = 2-Ph) (81FES441).

N-(1-Acetyl-3-methyl-5-pyrazolyl)aminomethylenemalonate (**1103**) was cyclized to pyrazolo[1,5-*a*]pyrimidine-6-carboxylate (**1102**, R = 2-Me) in 82% yield by heating in boiling diphenyl ether for 10 min (74AP177).

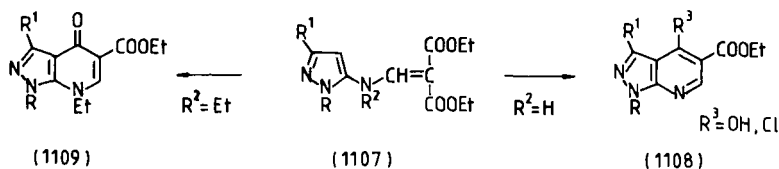
The ring closure of *N*-(1-substituted 3-pyrazolyl)aminomethylenemalonates (**1104**, R = Me, Et, R¹ = H) by heating in diphenyl ether at 220°C for 30 min afforded 2-substituted pyrazolo[3,4-*b*]pyridine-5-carboxylates (**1105**) in 67–71% yields (76GEP2617157; 77GEP2646670, 77USP-4038281, 77USP4038283).

At the same time, the cyclization of *N*-(1-substituted 3-pyrazolyl)aminomethylenemalonates (**1104**) by refluxing in a 1 : 4.4 mixture of polyphosphoric acid and phosphoryl chloride for 30 min gave 1-substituted pyrazolo[1,5-*a*]pyrimidine-6-carboxylates (**1105**) in good yields (83GEP-3309432).



1-Substituted pyrazolo[3,4-*b*]pyridine-5-carboxylates (**1108**, R³ = OH) were prepared in 44–86% yields on the cyclization of *N*-(1-substituted 5-pyrazolyl)aminomethylenemalonates (**1107**, R² = H) by heating in the melt at 240°C for 15 min or in diphenyl ether at 235–255°C for 15 min or in diphenyl ether at 235–255°C for 0.25–2 hr [68BRP1115254; 70GEP-2028869; 71GEP2028828, 71GEP2123318, 71GEP2125631, 71SAP887; 72GEP2138528, 72GEP2138529, 72GEP2159600, 72GEP2159601, 72JHC235, 72USP3669950; 73GEP2237765, 73GEP2258687, 73GEP2261444, 73GEP2301268; 74AP177, 74FRP2200003, 74GEP2333603, 74GEP2346466, 74GEP2356684, 74USP3840546; 75GEP2446495, 75USP3925388, 75USP3928362, 75USP3928368; 76USP3966746, 76USP3979399, 76USP3983128; 77CP1003419, 77USP4020072; 78IJC(B)161; 82JPR557; 83EUP94175, 83EUP96995; 86USP4563525; 87MI2; 89JMC2561].

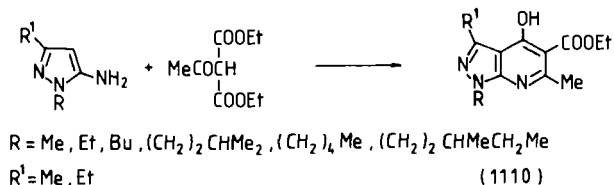
The cyclization of *N*-ethyl-*N*-(1-alkyl-5-pyrazolyl)aminomethylenemalonates (**1107**, R² = Et) by heating in a 2 : 1 mixture of acetic anhydride



and concentrated sulfuric acid gave 1-alkyl-7-ethylpyrazolo[3,4-*b*]pyrimidine-5-carboxylates (**1109**) in good yields [73JAP(K)81892].

4-Chloropyrazolo[3,4-*b*]pyridine-5-carboxylates (**1108**, $\text{R}^3 = \text{Cl}$) were prepared in 69–89% yields by the cyclization of *N*-(1-substituted 5-pyrazolyl)aminomethylenemalonates (**1107**, $\text{R} = \text{Me, Et, Ph}$, $\text{R}^1 = \text{H, Me, Ph}$, $\text{R}^2 = \text{H}$) by heating in boiling phosphoryl chloride for 4 hr or 10 hr (72JHC235; 73GEP2258687, 73GEP2301268; 74GEP2356684, 74USP3840546; 76USP3966746, 76USP3979399; 88CJC420).

The cyclocondensation of 1-alkyl-5-aminopyrazoles and diethyl 2-acylmalonates in polyphosphoric acid at 120–130°C for 1–3 hr gave ethyl 1-substituted 6-methylpyrazolo[3,4-*b*]pyrimidine-5-carboxylates (**1110**) in 48–80% yields (73GEP2237765, 73GEP2258687, 73GEP2261444; 74GEP-2333603; 75USP3925388; 82USP4364948; 83EUP94175; 86USP4463525; 89JMC2561).

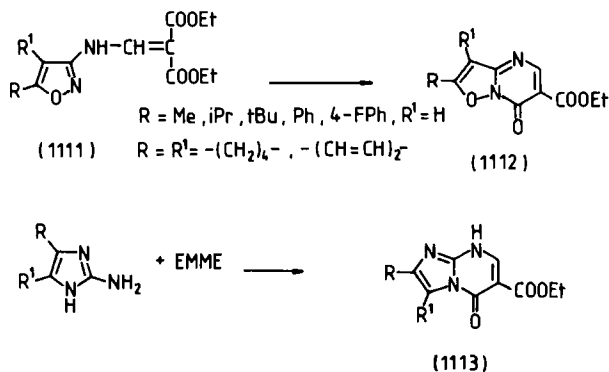


The cyclization of *N*-(1,2-isoxazol-3-yl)aminomethylenemalonates (**1111**) by heating in Dowtherm A gave isoxazolo[2,3-*a*]pyrimidinecarboxylates (**1112**) [82JAP(K)158789].

2-Amino-4,5-diphenylimidazole was reacted with EMME to give imidazo[1,2-*a*]pyrimidine-6-carboxylate (**1113**, $\text{R} = \text{R}^1 = \text{Ph}$) (51BSB69).

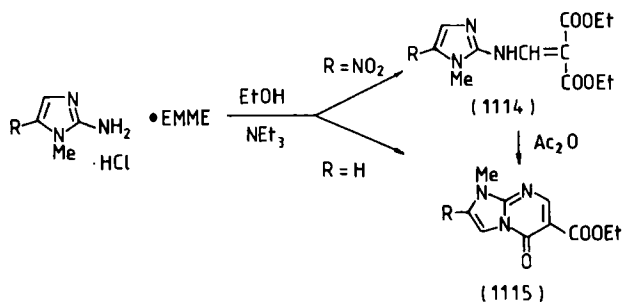
The reaction of 2-aminoimidazole and EMME in boiling acetic acid for 3–6 hr yielded ethyl imidazo[1,2-*a*]pyrimidine-6-carboxylate (**1113**, $\text{R} = \text{R}^1 = \text{H}$) (59JOC779).

The reaction of 2-amino-1-methylimidazole hydrochloride and EMME by heating in boiling ethanol in the presence of excess triethylamine overnight gave imidazo[1,2-*a*]pyrimidine-6-carboxylate (**1115**, $\text{R} = \text{H}$) in 47% yield [82IJC(B)1030]. The similar reaction with 5-nitro-2-amino-1-methylimidazole yielded only a condensation product (**1114**, $\text{R} = \text{NO}_2$), which



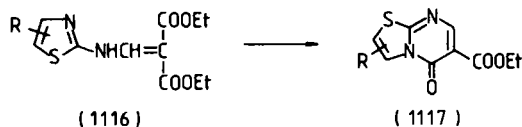
could be cyclized by the action of boiling acetic anhydride for 16 hr to imidazo[1,2-*a*]pyrimidine-6-carboxylate (**1115**, R = NO₂) in 18% yield.

2-Aminooxazole was reacted with EMME by heating in boiling trichlorobenzene for 2 hr to yield ethyl oxazolo[3,2-*a*]pyrimidine-6-carboxylate (73BRP1331059).



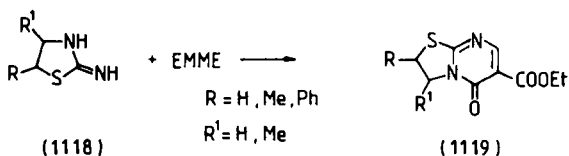
The heating of *N*-(4-methyl-2-thiazolyl)aminomethylenemalonate (**1116**, R = 4-Me) in the melt at 150–165°C for 20 hr (64IZV1481) or at 200–215°C for 30 min (54JPJ966), or the reaction of 4-methyl-2-aminothiazole and EMME at 200°C for 2.5 hr (54JPJ966), afforded 3-methylthiazolo[3,2-*b*]pyrimidine-6-carboxylate (**1117**, R = 3-Me).

2-Aminothiazoles were reacted with EMME in boiling trichlorobenzene (59JOC779; 72JMC1203; 73BRP1331059; 77GEP2648770) or in boiling ethanol for 5 hr (74CPB243) to give thiazolo[3,2-*a*]pyrimidine-6-carboxylates (**1117**). Compounds **1117** were also obtained in good yields on the cyclization of 2-thiazolylaminomethylenemalonates (**1116**) by heating in Dowtherm A at 215–230°C for 0.5–2.0 hr, and they were obtained in 24–26% yields in boiling toluene on the action of trifluoroacetic anhydride for 20–26 hr (81FRP2470132).

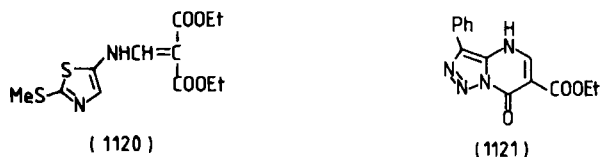


The reaction of 2-iminothiazolidines (**1118**) and EMME in boiling ethanol afforded dihydrothiazolo[3,2-*a*]pyrimidine-6-carboxylates (**1119**) in good yields (73GEP2241241; 76GEP2264979).

Diethyl *N*-(2-methylthio-4-thiazolyl)aminomethylenemalonate (**1120**) failed to cyclize thermally or on heating in phosphoryl chloride (84JHC1361).

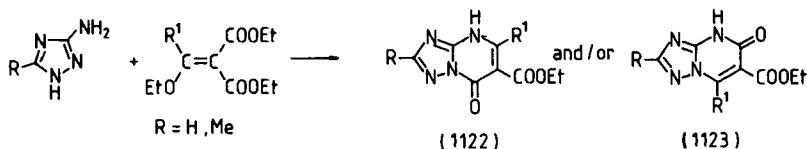


The reaction of 5-amino-4-phenyl-1,2,3-triazole and EMME in refluxing ethanol in the presence of piperidine for 40 hr gave 48% of *N*-(1,2,3-triazol-5-yl)aminomethylenemalonate (**67**) and 1% of 1,2,3-triazolo[1,5-*a*]pyrimidine-6-carboxylate (**1121**). When the reaction period was 96 hr, 25% of the bicyclic compound (**1121**) was obtained. The heating of *N*-(1,2,3-triazol-5-yl)aminomethylenemalonate (**67**) in boiling ethanol in the presence of piperidine afforded 95% of triazolo[1,5-*a*]pyrimidine-6-carboxylate (**1121**) [71JCS(C)2156].



Williams investigated the reactions between 3-amino-1,2,4-triazoles and EMME or 1-ethoxyethylidenemalonate (61JCS3046; 62JCS2222). He assumed that 3-amino-1,2,4-triazoles reacted with EMME or 1-ethoxyethylidenemalonate first via the primary amino group under acidic conditions, while under basic conditions, the ring nitrogen atom was involved in the first step of the cyclocondensation (61JCS3046).

In boiling acetic acid for 3 hr, 3-aminotriazole and diethyl 1-ethoxyethylidenemalonate gave 1,2,4-triazolo[1,5-*a*]pyrimidin-5-one (**1122**, R = H, R¹ = Me) in 39% yield. When this reaction was carried out in boiling



ethanol in the presence of sodium ethylate for 6 hr or in boiling pyridine in the presence of triethylamine overnight, the isomeric[1,2,4]triazolo[1,5-*a*]pyrimidin-5-one (**1123**, R = H, R¹ = Me) was obtained in 55% and 34% yields, respectively. A 2:3 mixture of isomeric bicycles **1122** and **1123** was obtained in 42% yield in boiling pyridine for 16 hr (61JCS3046).

The reactions of 5-methylthio-3-amino- or 3,5-diamino-1,2,4-triazole and diethyl 1-ethoxyethylidenemalonate in boiling ethanol in the presence of sodium ethylate for 1.5–3.5 hr gave 1,2,4-triazolo[1,5-*a*]pyrimidin-7-ones (**1123**, R = MeS, NH₂, R¹ = Me) in 44% and 20% yields, respectively. The reaction of 5-methylthio-3-amino-1,2,4-triazole (R = MeS) and 2-ethoxyethylidenemalonate in boiling pyridine for 4 hr gave 1,2,4-triazolo[1,5-*a*]pyrimidin-5-one (**1122**, R = MeS, R¹ = Me) in 12% yield (61JCS3046).

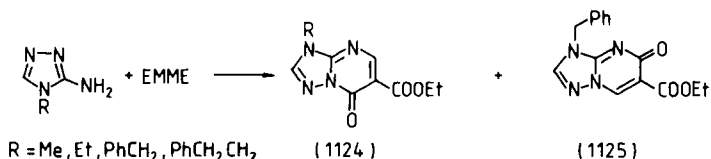
The reaction of 3-amino-1,2,4-triazole and EMME on heating in boiling trichlorobenzene (59JOC779), in boiling acetic acid (59JOC779; 62JCS2222), or in boiling ethanol in the presence of sodium ethylate (62JCS2222) gave 1,2,4-triazolo[1,5-*a*]pyrimidin-5-one (**1122**, R = R¹ = H). A mixture of **1122** and **1123** (R = MeS, R¹ = H) was obtained in the reaction of 5-methylthio-3-amino-1,2,4-triazole and EMME in boiling ethanol in the presence of sodium ethylate (62JCS2222).

[1,2,4]Triazolo[1,5-*a*]pyrimidin-7-ones (**1122**, R = H, MeS, R¹ = H) were also prepared by the cyclization of diethyl *N*-(1,2,4-triazol-3-yl)aminomethylenemalonate and 5-methylthio derivative (**24**) by heating in boiling acetic acid (62JCS2222).

5-Benzylthio-3-amino-1,2,3-triazole was reacted with EMME in boiling ethanol in the presence of sodium ethylate for 12–24 hr to give 1,2,4-triazolo[1,5-*a*]pyrimidin-5-one (**1122**, R = PhCH₂S, R¹ = H) in 67% yield (74GEP2327133; 82JMC420).

[1,2,4]Triazolo[1,5-*a*]pyrimidin-7-ones (**1122**, R = H, SH, COOH, COOMe, 2- or 4-pyridyl, R¹ = H) were prepared in moderate or good yields in the reaction of the appropriate 3-amino-1,2,4-triazole and EMME in boiling acetic acid for 3–18 hr [77GEP2648770; 80JCS(P1)1347; 85EUP150507; 87GEP3522463; 88IJC(B)825]. The mercapto derivative (**1122**, R = SH, R¹ = H) was obtained in higher yield (68% vs. 39%) when cyclocondensation was carried out in boiling ethanol in the presence of piperidine for 7 hr, and the reaction mixture was allowed to stand at room temperature overnight (85EUP150507).

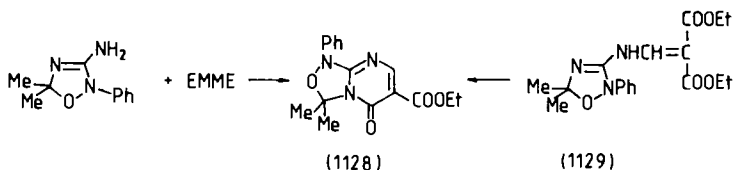
Spickett and Wright investigated the reactions of 4-substituted 3-amino-1,2,4-triazoles and EMME in acetic acid for 24–48 hr [67JCS(C)503]. Generally, they obtained [1,2,4]triazolo[1,5-*a*]pyrimidine-7-ones (**1124**) in 38–56% yields. In the case of the benzyl derivative (R = CH₂Ph), the isomeric triazolo[1,5-*a*]pyrimidin-5-one (**1125**) was also isolated from the mother liquor, in 5% yield. From the 4-ethyl and 4-phenethyl derivatives (R = Et, CH₂CH₂Ph), 1-(1,2,4-triazol-3-yl)pyridin-2-ones (**1126**) were also obtained in 1–2% yields.



In the reaction of 4-benzyl-3-amino-1,2,4-triazole and 1-ethoxyethylidenemalonate under the previous circumstances, 7-methyl-1,2,4-triazolo[1,5-*a*]pyrimidin-7-one (**1127**) was prepared in 10% yield [67JCS(C)503].



The reaction of 3-amino-5,5-dimethyl-2-phenyl-1,2,4-oxadiazoline and EMME at 100°C for 1 hr or the heating of *N*-(1,2,4-oxadiazolin-3-yl)aminomethylenemalonate (**1129**) at 120°C for 2 hr afforded [1,2,4]oxadiazolo[4,3-*a*]pyrimidine-6-carboxylate (**1128**) (63JCS6028).



N-(1,3,4-Oxadiazol-2-yl)aminomethylenemalonates (**1130**, X = O) were cyclized by heating the melt at 180–200°C under vacuum for 3–7 hr, or in boiling Dowtherm A for 10–30 min, to give [1,3,4]oxadiazolo[3,2-*a*]pyrimidine-6-carboxylates (**1131**, X = O) [67EGP56240; 70AP501; 88IJC(B)293].



1,3,4-Thiadiazolo[3,2-*a*]pyrimidine-6-carboxylates (**1131**, X = S, R = Me, Et) were obtained in good yields by the reaction of 2-amino-1,3,4-thiadiazoles and EMME in boiling trichlorobenzene for 1 hr (59JOC779; 73ABC1197). They were also obtained in 58% yield, by the cyclization of *N*-(1,3,5-thiadiazol-2-yl)aminomethylenemalonates (**1130**, X = S, R = Me, Et) by heating the melt at 150–160°C *in vacuo* for 11 hr, or in 25–88% yields in a mixture of polyphosphoric acid and phosphoryl chloride at 120°C for 30 min (84GEP3346223; 86FES737).

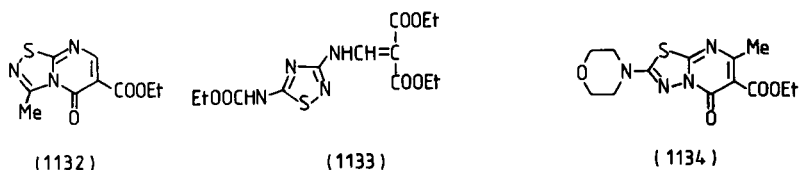
2-Amino-5-mercapto-1,3,4-thiadiazole was reacted with EMME in boiling DMF for 16 hr to afford thiadiazolo[3,2-*a*]pyrimidine-6-carboxylate (**1131**, X = S, R = SH) in 80% yield [85EUP150507].

2-Benzylthio-1,3,4-thiadiazolo[3,2-*a*]pyrimidine-6-carboxylate (**1131**, X = S, R = PhCH₂S) was prepared in 45% yield in the reaction of 2-amino-5-benzylthio-1,3,4-thiadiazole and EMME in polyphosphoric acid at 130–150°C for 15 min (87EUP238997).

5-Amino-3-methyl-1,2,4-thiadiazole was reacted with EMME in boiling trichlorobenzene to give 1,2,4-thiadiazolo[4,5-*a*]pyrimidine-6-carboxylate (**1132**) (59JOC779).

Instead of the corresponding cyclized product, only the *N*-(1,2,4-thiadiazol-3-yl)aminomethylenemalonate (**1133**) was obtained in 12% yield from the reaction of 3-amino-5-ethoxycarbonylamino-1,2,4-thiadiazole and EMME in polyphosphoric acid at 110°C for 3 hr (77JHC621).

The cyclocondensation of 2-amino-5-(4-morpholinyl)-1,3,4-thiadiazole and diethyl 1-ethoxyethylidenemalonate at 150°C for 20 min gave 7-methyl-1,3,4-thiadiazolo[3,2-*a*]pyrimidine-6-carboxylate (**1134**) in 34% yield (84GEP3346223).



The cyclocondensation of 2-amino-5-(4-morpholinyl and 3-pyridyl)-1,3,4-thiadiazoles and diethyl 1-ethoxyethylidenemalonate in diglyme at 140°C for 20 hr gave the corresponding ethyl 2-substituted 7-methyl-1,3,4-

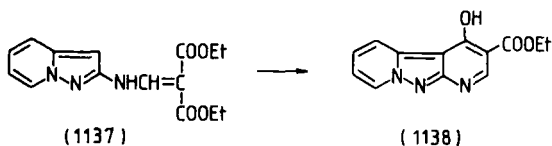
thiadiazolo[3,2-*a*]pyrimidine-6-carboxylates in 14–25% yields after column chromatography (86FES737). Reactions in ethanol or dimethylacetamide were unsuccessful.

5-Aminotetrazole did not react with EMME (59JOC779).

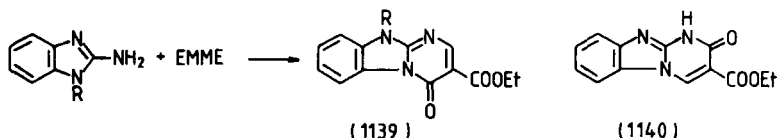
The ring closure of 3-indazolyaminomethylenemalonate (**1135**) by heating in diphenyl ether at 160°C for 1 hr (76T493) or in Gilotherm at 255°C for 10 min (78GEP2822124; 80MI3) afforded pyrimido[1,2-*b*]indazolecarboxylate (**1136**) in 73% and 90% yields, respectively.



The heating of *N*-(pyrazolo[1,5-*a*]pyridin-2-yl)aminomethylenemalonate (**1137**) in diphenyl ether at 240–250°C for 10 min afforded pyrido[1', 2' : 1,5]pyrazolo[3,4-*b*]pyridine-6-carboxylate (**1138**) in 69% yield [77JAP(K)17497, 77JAP(K)36695].



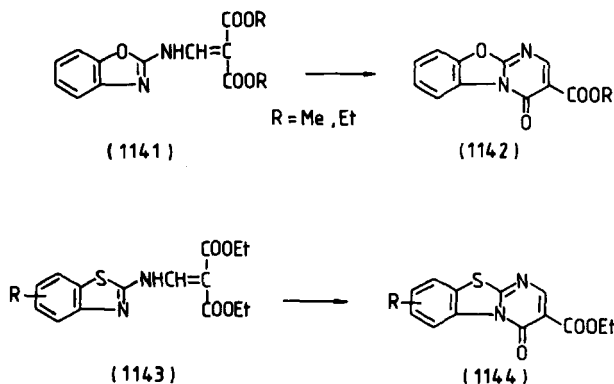
4-Oxypyrimido[1,2-*a*]benzimidazole-3-carboxylate (**1139**, R = H) was prepared in 27% yield by the reaction of 2-aminobenzimidazole and EMME by heating at 100°C for 5 min (72JMC1203), in 37% yield at 110°C for 30 min (73JHC71), in 51% yield in boiling ethanol for 5 hr (73CPB2019), in over 95% yield in boiling trichlorobenzene [73JCS(P1)1588], and in 95% yield in DMF at 80°C for 3 hr (78USP4072679, 78USP4109087, 78USP4109091). Earlier, it was stated that the reaction product was the isomeric 2-oxo derivative (**1140**) (51BSB69), but this was later corrected by Chow *et al.* (73JHC71).



10-Methylpyrimido[1,2-*a*]benzimidazole-3-carboxylate (**1139**, R = Me) was obtained in over 95% yield, in the reaction of 2-amino-1-methylbenzimidazole and EMME in boiling trichlorobenzene [73JCS(P1)1588], and in 63% yield in boiling methanol for 15 min (79JOC1811).

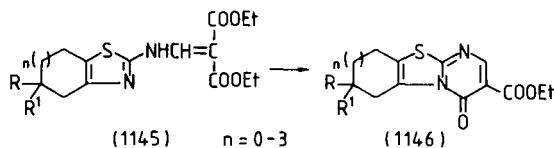
2-Benzoxazolylaminomethylenemalonates (**1141**) were cyclized by heating in boiling diphenyl ether, Dowtherm A, or trichlorobenzene for 1–4 hr to give pyrimido[2,1-*b*]benzoxazole-3-carboxylates (**1142**) in 61–90% yields (72JMC1203; 73CPB2019; 79JOC1811).

Pyrimido[2,1-*b*]benzothiazole-3-carboxylates (**1144**) were prepared in moderate or good yields by the cyclization of 2-benzothiazolylaminomethylenemalonates (**1143**) by heating in the melt at 190–210°C (68SAP7053, 68YZ1003) in refluxing acetic anhydride (68SAP7053), in boiling trichlorobenzene (72JMC1203), in boiling Dowtherm A (73CPB2019) or in refluxing diphenyl ether (79JOC1811), or by the cyclocondensation of 2-amino-benzothiazoles and EMME in boiling trichlorobenzene [71JCS(C)2094; 72JMC1203] or in Dowtherm A at 220°C (73JHC769).



8-Ethoxypyrimido[2,1-*b*]benzothiazole-3-carboxylate (**1144**, R = 8-EtO) was prepared in 74% yield in the reaction of 2-acetamido-6-ethoxybenzothiazole and EMME at 250–265°C for 1.5 hr (68YZ1003).

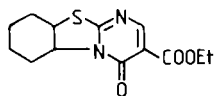
Cyclopentano(*g*)-, cyclohexano(*g*)-, and cyclooctano(*g*)thiazolo[3,2-*a*]pyrimidinecarboxylates (**1146**, R = R¹ = H) were obtained in good yields by heating the appropriate *N*-(cycloalkano(*d*)thiazol-2-yl)aminomethylenemalonate (**1145**) in Dowtherm A at 220–230°C for 25–120 min (81FRP2470132). Cyclohexano(*g*)thiazolo[3,2-*a*]pyrimidinecarboxylates (**1146**, *n* = 1, R = H, Me, R¹ = H, Me, Ph) were prepared in 68–84% yields by the cyclization of *N*-(cyclohexano(*d*)thiazol-2-yl)aminomethylenemalonates (**1145**, *n* = 1) by the action of trifluoroacetic anhydride in



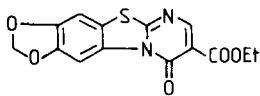
boiling toluene for 16–21 hr (81FRP2470132). Cycloheptano(g)thiazolo[3,2-*a*]pyrimidinecarboxylate (**1146**, $n = 2$, $R = R' = H$) was also prepared in 62% yield in the reaction of 2-aminocycloheptano(*d*)thiazole and EMME by heating in Dowtherm A at 220–230°C for 2 hr (81FRP2470132).

Hexahydropyrimido[2,1-*b*]benzothiazolecarboxylate (**1147**) was prepared in the reaction of 2-aminohexahydrobenzothiazole and EMME in boiling ethanol (73GEP2241241; 76GEP2264979). The stereochemistry of the compound was not determined.

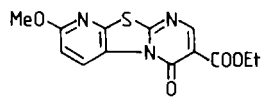
7,8-Methylenedioxy-pyrimido[2,1-*b*]benzothiazolecarboxylate (**1148**) and pyrido[3',2':4,5]thiazolo[3,2-*a*]pyrimidinecarboxylate (**1149**) were prepared in the reaction of 2-amino-5,6-methylenedioxybenzothiazole and 2-amino-6-methoxypyrido[2,3-*d*]thiazole with EMME in Dowtherm A at 220°C (73JHC769).



(1147)



(1148)



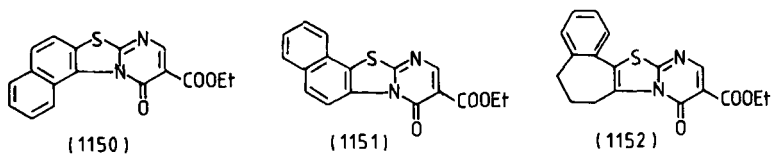
(1149)

Naphtho[1',2':4,5]- and naphtho[2',1':4,5]thiazolo[3,2-*a*]pyrimidinecarboxylates (**1150** and **1151**) were prepared by the cyclization of *N*-(naphtho[1,2-*d*]thiazol-2-yl)- and *N*-(naphtho[2,1-*d*]thiazol-2-yl)aminomethylenemalonates, by heating in acetic anhydride (68SAP7053). *N*-(Naphtho[1,2-*d*]thiazol-2-yl)aminomethylenemalonate was also cyclized in boiling trichlorobenzene (72JMC1203) or in refluxing Dowtherm A (85AP84).

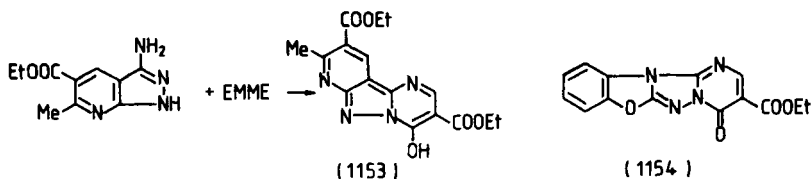
Tetracyclic nitrogen bridgehead pyrimidinecarboxylate (**1152**) was obtained in 49% yield by the cyclization of *N*-(benzo[4,5]cyclohepta[*d*]thiazol-2-yl)aminomethylenemalonate in boiling diphenyl ether for 0.5 hr (69NKZ569).

3-Aminopyrazolo[3,4-*b*]pyridine was reacted with EMME in acetic acid to give pyrido[2',3':3,4]pyrazolo[1,5-*a*]pyrimidine-3,9-dicarboxylate (**1153**) in 95% yield [77IJC(B)349].

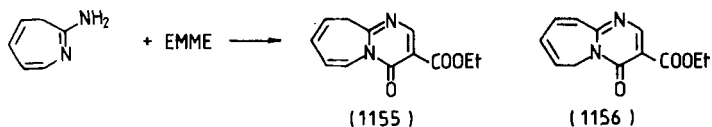
The heating of *N*-(1,2,4-triazolo[3,4-*b*]benzoxazol-3-yl)aminomethy-



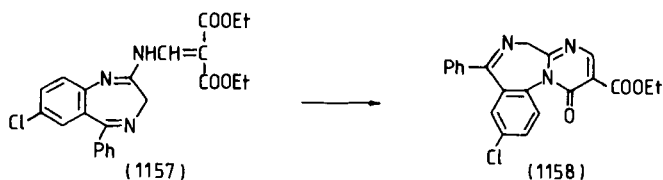
lenemalonate (**99**) in boiling xylene for 4 hr afforded pyrimido[1',2' : 1,5]-1,2,4-triazolo[3,4-*b*]benzoxazole-3-carboxylate (**1154**) in 70% yield. The tetracyclic compound (**1154**) was obtained in 68% yield in a one-pot procedure when 3-amino-1,2,4-triazolo[3,4-*b*]benzoxazole and EMME were reacted in boiling xylene for 8 hr (89H925).



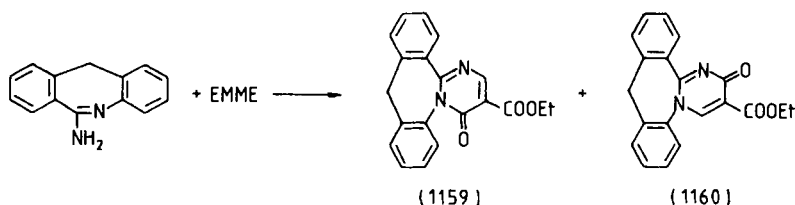
The cyclocondensation of 2-amino-3*H*-azepine and EMME in boiling butanol for 1 hr gave a roughly 3 : 1 mixture of the isomeric 4*H*,10*H*- and 4*H*,6*H*-pyrimido[1,2-*a*]azepine-3-carboxylates (**1155** and **1156**) in 68% yield. The isomers could be separated by fractional crystallization. 4*H*,6*H*-Pyrimido[1,2-*a*]azepine-3-carboxylate (**1156**) was probably formed from the 4*H*,10*H* isomer (**1155**) in a symmetry-allowed [1,5]-sigmatropic shift (84H2285).



The ring closure of *N*-(3*H*-1,4-benzodiazepin-2-yl)aminomethylene-malonate (**1157**) by heating in Dowtherm A at 240–248°C for 10 min afforded pyrimido[1,2-*a*]-1,4-benzodiazepinecarboxylate (**1158**) in 56% yield (74GEP2400449).

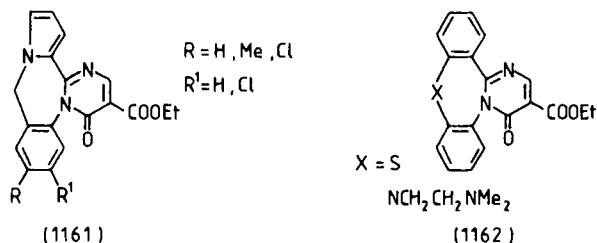


6-Aminomorphanthridine was reacted with EMME in 1,2,4-trichlorobenzene under nitrogen at 100°C for 1 hr, then at reflux temperature for 3 hr, to give 53% of dibenzo[*c,f*]pyrimido[1,2-*a*]azepin-4-one (**1159**) and 1% of dibenzo[*c,f*]pyrimido[1,2-*a*]azepin-2-one (**1160**) (80JHC341).



The thermal cyclization of *N*-(5*H*-pyrrolo[2,1-*c*]-1,4-benzodiazepin-11-yl)aminomethylenemalonates (**97**) by heating in boiling Dowtherm A for 1–2 hr gave 10*H*-pyrimido[1,2-*a*]pyrrolo[2,1-*c*]-1,4-benzodiazepine-3-carboxylates (**1161**) in 68–86% yields (85CP1197242, 85JHC305). Compound **97** ($R = R^1 = H$) was also cyclized in ethanol in the presence of sodium ethoxide at ambient temperature to afford tetracyclic compound **1161** ($R = R^1 = H$) in 87% yield (85CP1197242, 85JHC305).

The ring closure of *N*-dibenzo[*b,f*]-1,4-thiazepin-11-yl- and [5-(2-dimethylaminoethyl) - 5*H* - dibenzo[*b,f*] - 1,4 - diazepin - 11 - yl]amino - methylenemalonates (**95**, $X = S$, $N-CH_2CH_2NMe_2$) was carried out in boiling trichlorobenzene for 3–4 hr to give tetracyclic nitrogen bridgehead derivatives (**1162**, $X = S$, $N-CH_2CH_2NMe_2$) in good yields (80JHC341).

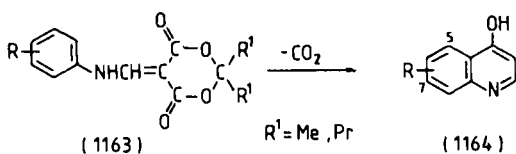


B. Cyclization of Alkylidene Aminomethylenemalonates

1. INTRODUCTION

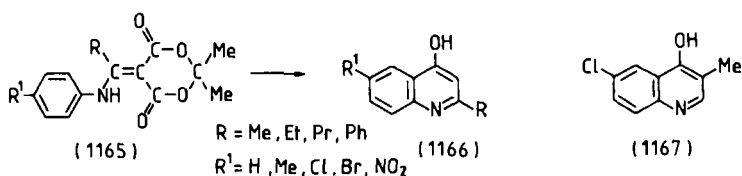
The heating of cycloalkylidene phenylaminomethylenemalonates (**1163**) in the melt at 245°C, in Dowtherm A between 175–245°C, in dibenzyl ether at 250°C, or in boiling nitrobenzene for a few minutes, gave 4-hydroxyquinolines (**1164**) [e.g., 69BRP1147760; 87T4803; 88JAP(K)-239269].

When (3-substituted phenyl)aminomethylenemalonate (**1163**, 3-R = H) was applied, a mixture of 5-substituted and 7-substituted 4-hydroxyquinolines (**1164**, 5-R ≠ H and 7-R ≠ H) was obtained. For example, the thermal cyclization of (3-nitrophenyl)aminomethylenemalonate in dibenzyl ether at 250°C afforded a 3 : 1 mixture of 7-nitro- and 5-nitro-4-hydroxyquinolines (**1164**, R = 7-NO₂ and 5-NO₂). 4-Hydroxyquinolines (**1164**) could also be prepared when a mixture of anilines, triethyl orthoformate, and isopropylidene malonate was slowly heated to 100°C in Dowtherm A, stirred over a period of 30 minutes, and then raised to a temperature of 250°C.

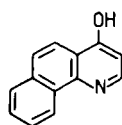


The cyclization of isopropylidene 1-(phenylamino)alkylidenemalonates (**1165**) in diphenyl ether at 250–260°C under nitrogen, or in boiling Dowtherm A, gave 2-substituted 4-hydroxyquinolines (**1166**) in 63–96% yields (69BRP1147760; 87S482).

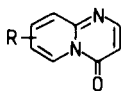
When the reaction mixture of 4-chloroaniline, triethyl orthoformate, and isopropylidene methylmalonate in Dowtherm A was heated slowly, stirred to reflux, and maintained at reflux for 3 minutes, 6-chloro-4-hydroxy-3-methylquinoline (**1167**) was obtained (69BRP1147760).



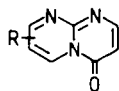
Similarly, 4-hydroxybenzo[*h*]quinoline (**1168**) (69BRP1147760), pyrido[1,2-*a*]pyrimidin-4-ones (**1169**) [69BRP1147760; 75USP3907798; 77JCS-(P1)789; 85JHC481, 85SC125; 86EUP218423; 89TL1529], pyrimido[1,2-*a*]pyrimidin-4-ones (**1170**) (69BRP1147760), pyrimido[1,2-*c*]pyrimidine (**1171**) (89TL1529), 5-hydroxypyrido[2,3-*d*]pyrimidines (**1172**, $R \neq H$) (84USP4432981), pyrimido[1,2-*b*]pyridazin-4-ones (**1173**) (69BRP1147760; 83H2225; 88JHC1535), pyrazino[1,2-*a*]pyrimidin-4-one (**1174**) (69BRP1147760), thiazolo[3,2-*a*]pyrimidin-5-one (**1175**) (85SC125), pyrazolo[1,5-*a*]pyrimidin-7-one (**1176**) (85BEP902150), pyrimido[1,2-*a*]quinoline (**1177**) (69BRP1147760; 75USP3907798), 10-hydroxy-4-oxo-4*H*-pyrano[2,3-*f*]quinoline (**1178**) (69BRP1147760), 4-hydroxy-1,7-naphthyridine (**1179**) (69BRP1147760), and pyrimido[1,2-*c*]quinazolinone (**1180**) (81EUP30156) were prepared by thermal cyclization of the corresponding isopropylidene (het)arylaminomethylenemalonates.



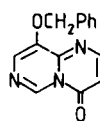
(1168)



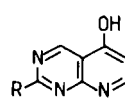
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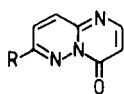
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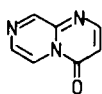
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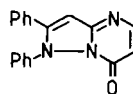
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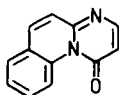
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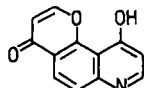
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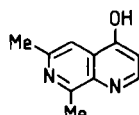
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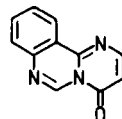
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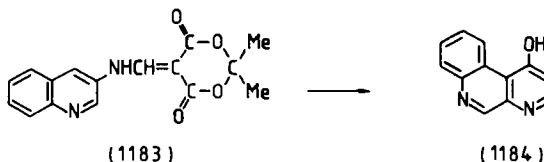
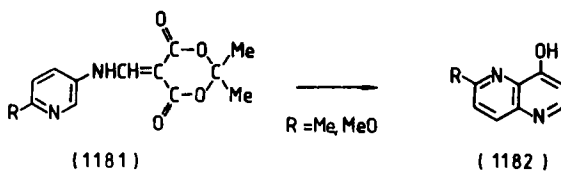
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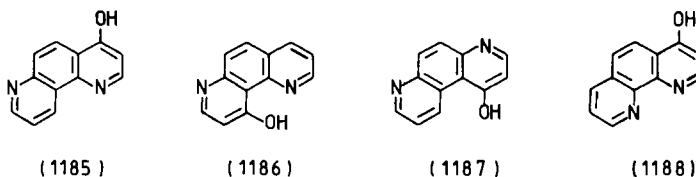
(1180)

The thermal cyclization of isopropylidene 3-pyridylaminomethylenemalonate (**1181**) afforded 4-hydroxy-1,5-naphthyridine (**1182**), while that of isopropylidene 3-quinolinylaminomethylenemalonate (**1183**) gave 1-hydroxybenzo(*f*)-1,7-naphthyridine (**1184**) (69BRP1147760).

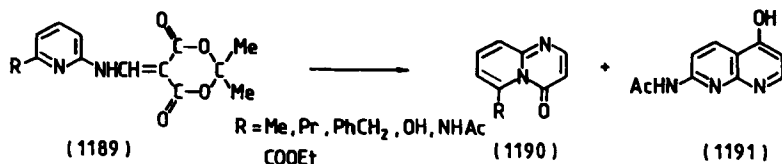
4-Hydroxy-1,7-phenanthroline (**1185**), 10-hydroxy-1,7-phenanthroline



(1186), 1-hydroxy-4,7-phenanthroline (1187), and 4-hydroxy-1,10-phenanthroline (1188) were prepared by the thermal ring closure of isopropylidene 5-, 6-, 7-, and 8-quinolynylaminomethylenemalonate, respectively, in boiling Dowtherm A for 3–5 min (69BRP1147760).



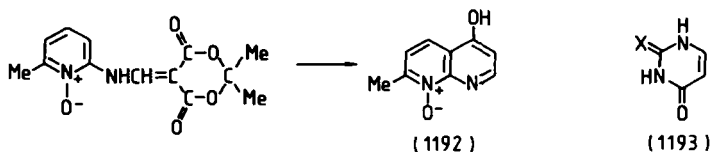
The cyclization of isopropylidene *N*-(6-substituted 2-pyridyl)amino-methylenemalonates (1189), by heating in mineral oil or in Dowtherm A, generally afforded 6-substituted pyrido[1,2-*a*]pyrimidin-4-ones (1190), except for the 6-acetamido derivative (1189, R = NHAc) which, in boiling Dowtherm A for about 5 min, gave a 1 : 1 mixture of 6-acetamidopyrido[1,2-*a*]pyrimidin-4-one (1190, R = NHAc) and 7-acetamido-4-hydroxy-1,8-naphthyridine (1191) in 86% yield (69BRP1147760; 75USP3907798; 85JHC481). However, when 1189 (R = NHAc) was added to preheated Dowtherm A with a reaction period of 4 min, 79% of pyrido[1,2-*a*]pyrimidin-4-one (1190, R = NHAc) and 6% of 1,8-naphthyridine (1191) were



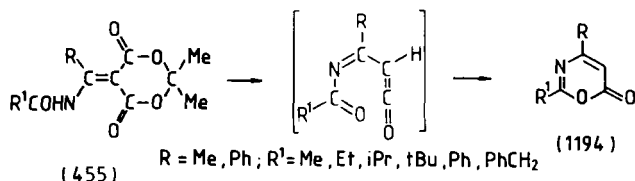
obtained, while in 1 min, 87% of **1190** ($R = \text{NHAc}$) and only 2% of **1191** were prepared [77JCS(P1)789].

The ring closure of isopropylidene *N*-(6-methyl-2-pyridyl)aminomethylenemalonate *N*-oxide by heating in diethyl phthalate at 275°C for 2 min gave 1,8-naphthyridine *N*-oxide (**1192**) (74USP3856800, 74USP3857851; 75USP3869464, 75USP3873554, 75USP3876650, 75USP3882132).

The thermal ring closure of isopropylidene *N*-[amino(thio)carbonyl]aminomethylenemalonates (**439**, $X = \text{O}, \text{S}$) in boiling diphenyl ether for 5 min afforded uracil and thiouracil (**1193**, $X = \text{O}, \text{S}$) in 68% and 70% yields, respectively (84SC961).



The thermolysis of isopropylidene acylaminomethylenemalonates (**455**) in the melt at 160–190°C for about 10 min, or in boiling decalin for 2 hr, gave 1,3-oxazin-6-ones (**1194**) in 36–93% and 33–74% yields, respectively (86CPB1980).



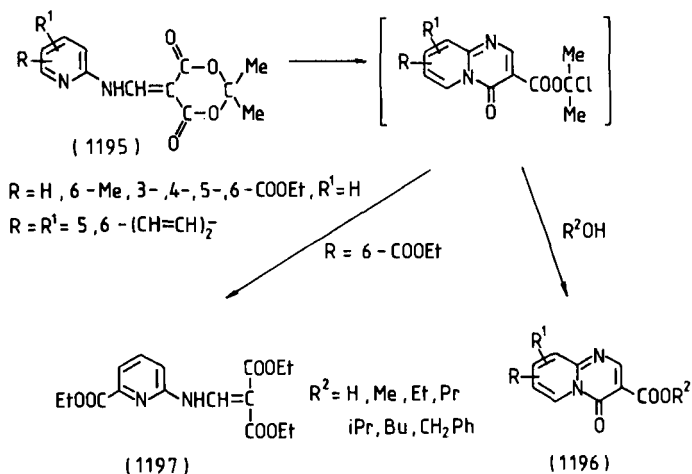
Rosoxacin was obtained in 16% yield by the cyclization of isopropylidene *N*-ethyl-*N*-[3-(4-pyridinyl)phenyl]aminomethylenemalonate in polyphosphoric acid at 125–137°C for 30 min [77JAP(K)116460].

Isopropylidene 2-pyridyl- and 2-quinolinylaminomethylenemalonates (**1195**) were cyclized in boiling phosphoryl chloride by the action of polyphosphoric acid at 135–140°C. When the formation of hydrogen chloride gas ceased, the reaction mixtures were treated with an alcohol or water to afford the corresponding alkyl 4-oxopyrido[1,2-*a*]pyrimidine-3-carboxylates or alkyl 1-oxopyrimido[1,2-*a*]quinoline-2-carboxylates (**1196**, $R^2 = \text{alkyl}$) in 51–96% yields or to afford carboxylic acids (**1196**, $R^2 = \text{H}$) in 64–84% yields (79MIP2; 80MIP3; 84S152).

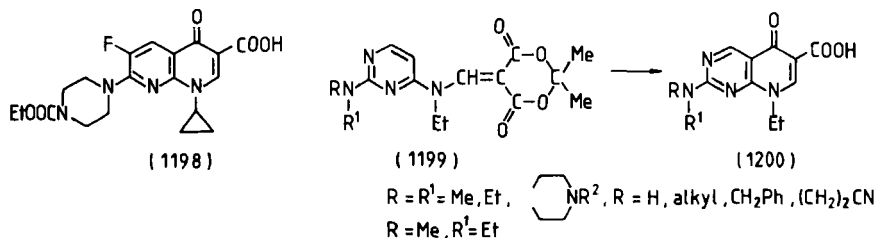
The 6-ethoxycarbonyl derivative (**1195**; $R = 6\text{-COOEt}$; $R^1 = \text{H}$) gave

diethyl *N*-(6-ethoxycarbonyl-2-pyridinyl)aminomethylenemalonate (**1197**) in 48% yield (84S152).

Isopropylidene *N*-cyclopropyl-*N*-[6-(4-ethoxycarbonylpiperazin-1-yl)-5-fluoropyridin-2-yl]aminomethylenemalonate (**428**) was cyclized in a mixture of acetic anhydride and concentrated sulfuric acid at 50–60°C for 2 hr to give 1,8-naphthyridine-3-carboxylic acid (**1198**) in 68% yield (85EUP153163, 85EUP153828, 85EUP159174; 86EUP172651; 88EUP-265230).



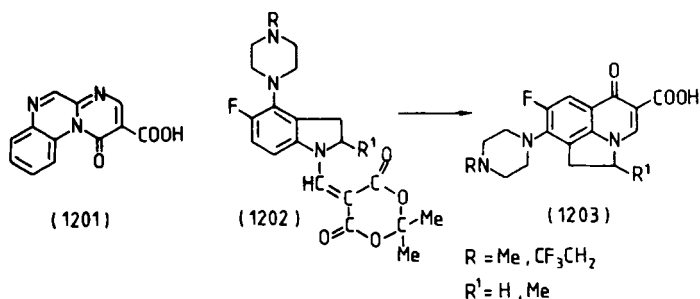
Isopropylidene *N*-ethyl-*N*-(4-pyrimidinyl)aminomethylenemalonates (**1199**) were cyclized by heating in a mixture of polyphosphoric acid and phosphorus pentoxide at 100°C for 1 hr to give pyrido[2,3-*d*]pyrimidine-6-carboxylic acids (**1200**) in 50–65% yields [83JAP(K)23692]. Higher yields (~86%) were achieved when the cyclizations were carried out in polyphosphate [83JAP(K)72583].



When *N*-ethyl-*N*-[2-(4-benzylpiperazin-1-yl)pyrimidin-4-yl]aminomethylenemalonate [**1199**, $\text{PhCH}_2\text{N}(\text{CH}_2\text{CH}_2)_2$] was heated in polyphosphoric acid at 190–200°C for 5 min, and the reaction mixture was treated with aqueous sodium hydroxide, pyrido[2,3-*d*]pyrimidinecarboxylic acid [**1200**, $\text{R} = \text{R}' = \text{PhCH}_2\text{N}(\text{CH}_2\text{CH}_2)_2$] was obtained in 20% yield [81JAP(K)99480].

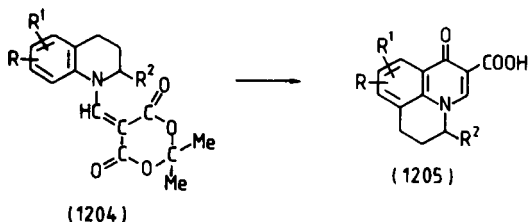
Isopropylidene 2-quinoxalinyaminomethylenemalonate was treated in methylene chloride with polyphosphoric acid at 60°C to give pyrimido[1,2-*a*]quinoxaline-2-carboxylic acid (**1201**) in 97% yield (83EUP86723).

The cyclization of isopropylidene 1-indolinylmethylenemalonates (**1202**) was carried out in polyphosphoric acid at 100°C to yield pyrrolo[3,2,1-*ij*]quinoline-2-carboxylic acids (**1203**) [82BEP891046, 82BEP891537; 83JAP(K)90511]. Further pyrrolo[3,2,1-*ij*]quinolinecarboxylic acids were prepared similarly, in 82–86% yields [82BEP891046, 82BEP891537, 82JAP(K)2285].



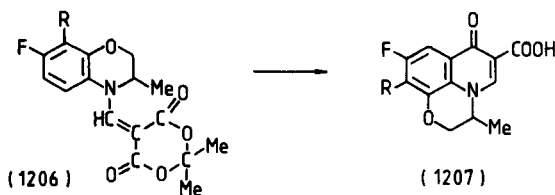
Benzo[*ij*]quinolizine-2-carboxylic acids (**1205**) were also obtained in good yields by the cyclization of isopropylidene 1-tetrahydroquinolinylmethylenemalonates (**1204**) by the action of polyphosphoric acid at 100–130°C for 0.5–1 hr [82BEP891046, 82BEP891537, 82JAP(K)2285, 82JAP(K)16882; 83JAP(K)90511].

Flumequine was prepared in 84% yield by the cyclization of isopropylidene (6-fluoro-2-methyl-1,2,3,4-tetrahydroquinolin-1-yl)methylenemalonate in polyphosphoric acid at 120–130°C for 30 min [82JAP(K)2285].

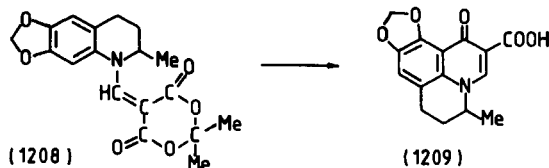


Isopropylidene (1,4-benzoxazin-4-yl)methylenemalonate (**1206**, R = Ac) was heated in polyphosphoric acid at 65°C for 2 hr to give pyrido[1,2,3-*de*]-1,4-benzoxazine-6-carboxylic acid (**1207**, R = Ac) in 57% yield (84EUP106489; 85EUP153163).

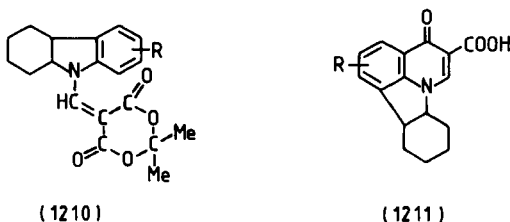
Pyrido[1,2,3-*de*]-1,4-benzoxazine-6-carboxylic acid (**1207**, R = F) was prepared in 93% yield by the cyclization of isopropylidene (1,4-benzoxazin-4-yl)methylenemalonate (**1206**, R = F) in a mixture of concentrated sulfuric acid and acetic anhydride [84JAP(K)122493]. Compound **1207** was also prepared in 58% yield in a mixture of concentrated sulfuric acid and acetyl chloride [84JAP(K)216890].



Isopropylidene (6,7-methylenedioxytetrahydroquinaldin-1-yl)methylenemalonate (**1208**) was cyclized by heating in polyphosphoric acid at 120–130°C for 1 hr to yield the tetracyclic carboxylic acid (**1209**) [82JAP(K)16882].

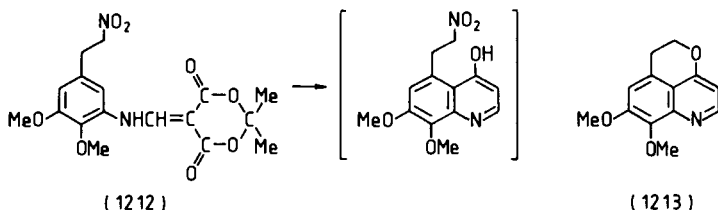


Pyrido[3,2,1-*jk*]carbazolecarboxylic acids (**1211**) were prepared in good yields by the cyclization of isopropylidene 9-hexahydrocarbazolylmethylenemalonates (**1210**) on the action of polyphosphoric acid, prepared from



phosphorus pentoxide and phosphoric acid, at 120–140°C for 30–40 min [82JAP(K)16882].

The heating of isopropylidene arylaminomethylenemalonate (**1212**) in boiling diphenyl ether under nitrogen for 5 min gave tricyclic pyrano[2,3,4-*de*]quinoline (**1213**) in 66% yield after flash column chromatography (87T4803).

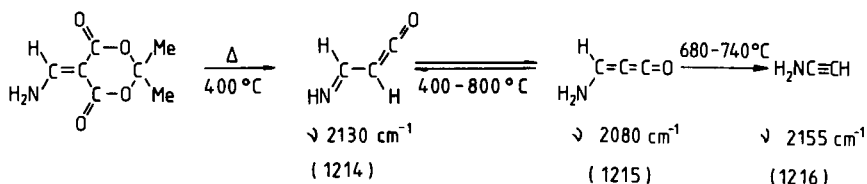


2. FLASH VACUUM PYROLYSIS OF ISOPROPYLIDENE AMINOMETHYLENEMALONATES

Flash vacuum pyrolysis (at 10^{-5} – 10^{-3} torr and 370–800°C) of isopropylidene aminomethylenemalonate gave a wide variety of products, and the mechanism of this reaction was investigated by several authors.

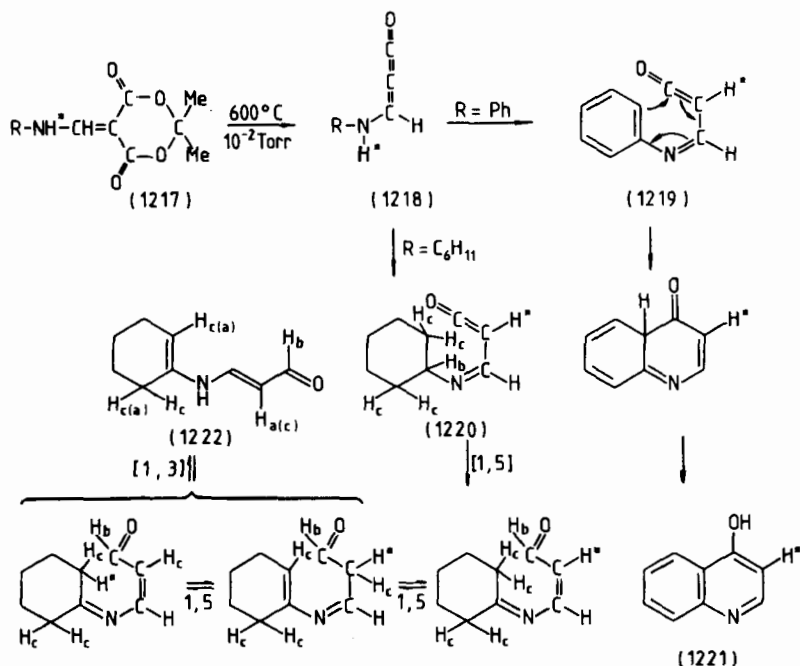
Wentrup *et al.* demonstrated the formation of imidoalkene (**1214**), methyleneketene (**1215**), and ethynamine (**1216**) during the flash vacuum pyrolysis (10^{-5} torr) of isopropylidene aminomethylenemalonate by collision activation mass spectroscopy and IR spectroscopy (88JA1337). The imidoalkene (**1214**) appeared first at a pyrolysis temperature of 390°C. As the temperature was increased, the imidoalkene (**1214**) was rapidly converted into methyleneketene (**1215**). The formation of ethynamine (**1216**) was prominent in the temperature range 680–740°C, and it was accompanied by a sharp decrease in the signal of methyleneketene (**1215**), whereas the imidoalkene (**1214**) was less affected. Compounds **1214**–**1216** were stable at -196°C , but they polymerized on warm-up.

McNab and his co-workers reported that the pyrolysis of monosubsti-

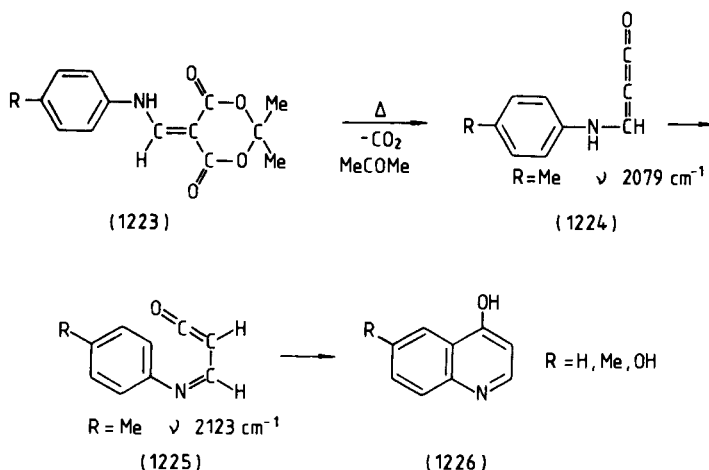


tuted aminomethylenemalonates (**1217**) is controlled by tautomerization of the intermediates (**1218**) to give imidoalkynes (**1219** and **1220**) [83CC957; 84JCS(P1)2129]. Imidoalkynes (**1219** and **1220**) were trapped by an aromatic ring or by sequences of 1,5-hydrogen shifts (Scheme 47). Thus, a phenylamino derivative (**1217**, R = Ph) gave 4-hydroxyquinoline (**1221**), and a cyclohexylamino derivative (**1217**, R = cyclohexyl) gave (cyclohexylamino)acrylaldehyde (**1222**). The suggested mechanism for the formation of (cyclohexylamino)acrylaldehyde (**1222**) was justified by the use of deuteriated (cyclohexylamino)methylenemalonates (**1217**, R = cyclohexyl deuteriated at positions *, b, and c) [84JCS(P1)2129].

Wentrup and co-workers also studied the flash vacuum pyrolysis of isopropylidene (monosubstituted amino)methylenemalonates (84JOC-2772). The pyrolysis of isopropylidene phenylaminomethylenemalonates (**1223**) between 400 and 600°C under a pressure of 10^{-5} – 10^{-3} torr afforded 4-hydroxyquinolines (**1226**) in 57–66% yields. The intermediates (**1224** and **1225**) of the pyrolysis of isopropylidene phenylaminomethylenemalonates (**1223**) could be isolated at -196°C on KBr or BaF₂ windows in a special apparatus allowing direct IR spectroscopic examination of the pyrolysates



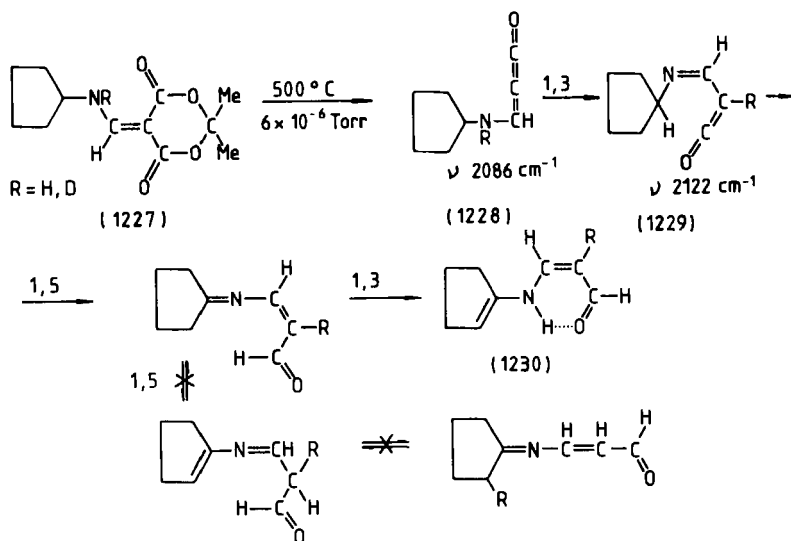
SCHEME 47



SCHEME 48

(Scheme 48). The very slow pyrolysis of the (4-methylphenyl)amine derivative (**1223**, R = Me) at 540°C and 10^{-5} torr resulted in IR absorption at 2079 cm^{-1} , indicating the presence of methyleneketene (**1224**, R = Me). Under less carefully controlled pyrolysis conditions at higher pressure, the 2079 cm^{-1} absorption was accompanied by an absorption at 2123 cm^{-1} , pointing to the presence of imidoalkene (**1225**, R = Me). Above 600°C, both intermediates disappeared and quinoline (**1226**, R = Me) was the only product.

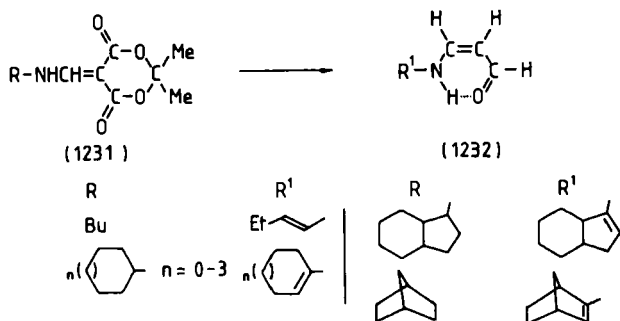
In the case of isopropylidene cyclopentylaminomethylenemalonate (**1227**, R = H), the presence of the methyleneketene (**1228**, R = H) at 500°C (6×10^{-6} torr) was supported by the IR absorption at 2086 cm^{-1} , recorded at -196°C . The imidoalkene (**1229**, R = H) was observed as a weak band (together with a stronger band for **1228**) at 2122 cm^{-1} at a pyrolysis temperature of 370°C (84JOC2772) (Scheme 49). An experiment was also carried out with the *N*-deuterio derivative (**1227**, R = D). In contrast with the experiment of McNab *et al.* (83CC957) (see previously), deuterium was present at position 2 of the acrylaldehyde side-chain (**1230**). No occurrence of deuterium in the pyrrolidine ring was detected. It was suggested that the hydrogen shift observed by McNab *et al.* must succeed the formation of the enaminoacrolein to give a product deuteriated in the ring. This could happen in McNab's experiments because the pressure in the flash vacuum pyrolysis apparatus used by McNab (10^{-2} torr) was significantly higher than that in Wentrup's study (10^{-4} – 10^{-6} torr). This led



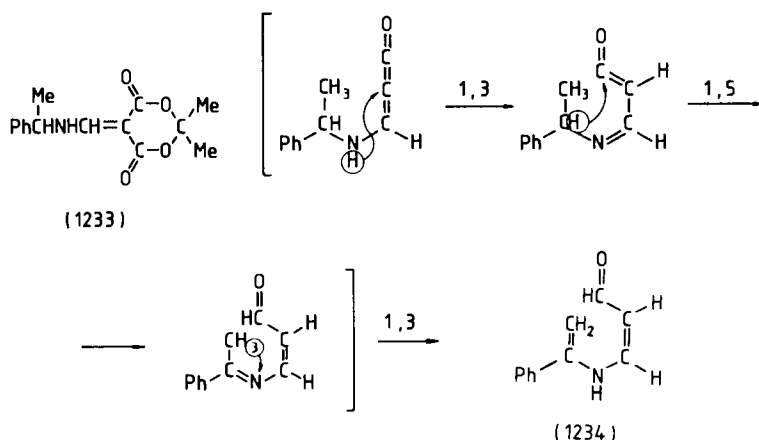
SCHEME 49

to a longer contact time and to more collisions with the walls, which might catalyse the hydrogen shifts.

The preparative pyrolyses of aliphatic and cycloaliphatic aminomethylene malonates (**1231**) afforded enaminoacroleins (**1232**) in 44–91% yields (84JOC2772).

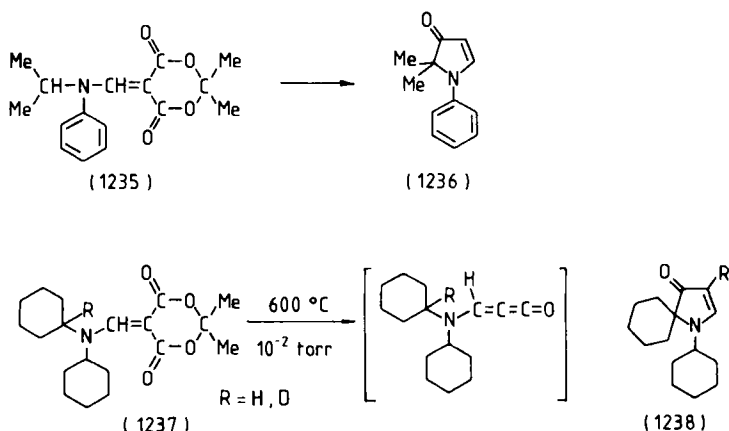


The pyrolysis of isopropylidene *N*-(α -methylbenzyl)aminomethylene malonate (**1233**) at 600°C and 10^{-2} torr gave 3-(1-phenylethylidene)aminoacrylaldehyde (**1234**) in 46% yield [84JCS(P1)2129].



The flash vacuum pyrolysis of isopropylidene *N,N*-disubstituted aminomethylenemalonates (e.g., **1235**, **1237**) was studied by McNab *et al.* [83CC957; 85CC213; 86JCS(P1)1465; 87CC138; 88JCS(P1)863, 88JCS(P1)869, 88JCS(P2)759]. They obtained 1,5,5-trisubstituted 2-pyrrolin-4-ones (e.g., **1236**, **1238**) in 38–75% yields.

Hydrogen transfer occurred on the pyrolysis of the monodeuteriated (dicyclohexylamino)methylenemalonate (**1237**, R = D) [83CC957; 86-JCS(P1)1465]. It was revealed by NMR spectroscopy that the transferred deuterium was located exclusively at C(3) of the pyrrolinone moiety (**1238**, R = D). The copyrolysis of compounds **1235** and **1237** (R = D) showed

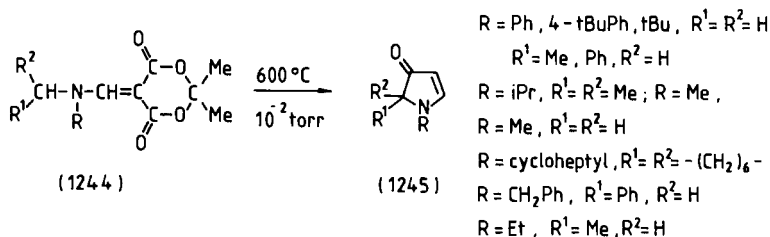


that the hydrogen transfer was a highly specific intramolecular process. The observed isotope effect (k_H/k_D) was ~ 1.9 , which indicated that the hydrogen transfer was rate-determining. The isotope effect seemed to be independent of temperature between 500–600°C [86JCS(P1)1465].

In a study of the flash vacuum pyrolysis of chiral isopropylidene *N*-isopropyl-*N*-(α -methylbenzyl)aminomethylenemalonates, (*R*)- and (*S*)- (**1239**), McNab and Monahan demonstrated the existence of another intermediate (**1242**) in the reaction pathway from the methyleneketene (**1240**) to the pyrrolinone (**1243**) [87CC138; 88JCS(P1)869]. Pyrolysis of the enantiomers (*R*) and (*S*) of compound **1239** resulted in the formation of an enantiomeric mixture of 1-isopropyl-5-methyl-5-phenyl-2-pyrrolin-5-one (**1243**), where incomplete chirality loss was observed (see Scheme 50).

Flash vacuum pyrolysis of other isopropylidene *N,N*-disubstituted aminomethylenemalonates (**1244**) also gave 1-substituted pyrrolin-4-ones (**1245**) [84HCA1402; 85CC213; 88JCS(P1)863].

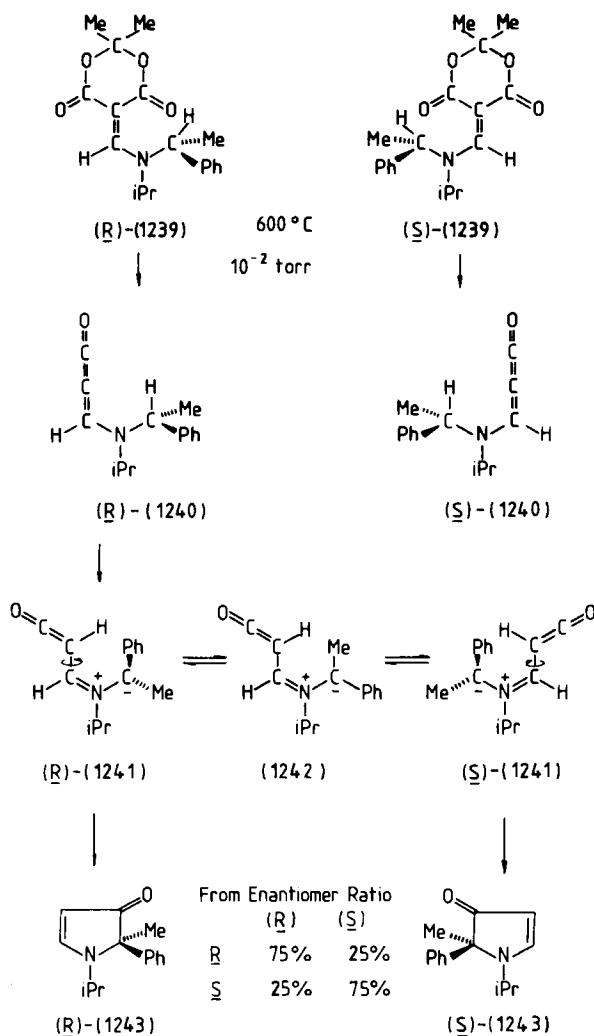
When *N*-[^{13}C]methyl-*N*-phenylaminomethylenemalonate (**1244**, $\text{R} = \text{Ph}$, $\text{R}^1 = \text{R}^2 = \text{H}$) was used, the 1-phenylpyrrolin-4-one (**1245**, $\text{R} = \text{Ph}$, $\text{R}^1 = \text{R}^2 = \text{H}$) labeled at position 5 with ^{13}C was obtained in 40% yield (88JCS(P2)759).



Generally, little regioselectivity was observed when unsymmetrical di-substituted aminomethylenemalonates (**1246**) were pyrolysed, but the *N*-methyl derivative (**1246**, $\text{R} = \text{R}^1 = \text{H}$) gave a mixture of **1247** and **1248** ($\text{R} = \text{R}^1 = \text{H}$) with a predominance of the 1-substituted 2-unsubstituted pyrrolone (**1247**, $\text{R} = \text{R}^1 = \text{H}$) [88JCS(P1)863]. Perhaps the reaction was sensitive to steric effects. *N*-Benzyl derivatives (**1246**, $\text{R} = \text{H}$, $\text{R}^1 = \text{Ph}$) gave only 2-phenylpyrrolinones (**1247**, $\text{R} = \text{H}$, $\text{R}^1 = \text{Ph}$) [88JCS(P1)863].

The pyrolysis of isopropylidene *N,N*-bis-(α -methylphenyl)aminomethylenemalonates (**1249**) afforded a 68 : 32 diastereomeric mixture of **1250** and **1251** in 13% yield [88JCS(P1)869].

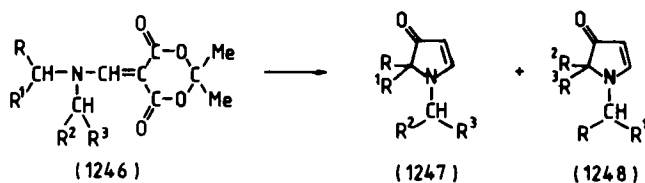
The flash vacuum pyrolysis of isopropylidene (cyclic amino)methylenemalonates yielded nitrogen bridgehead bicycles. The pyrolysis of the 2-methyl- and *cis*-2,6-dimethylpiperidino derivatives (**1252** and **1255**) gave



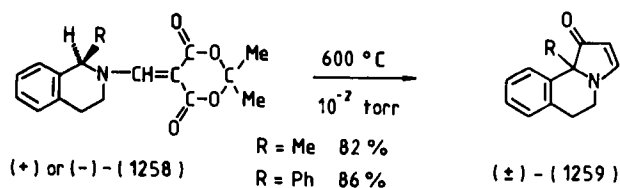
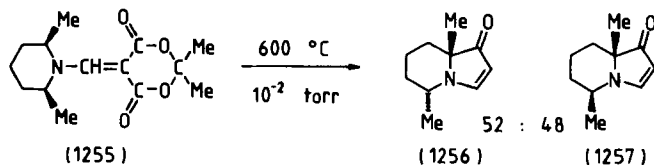
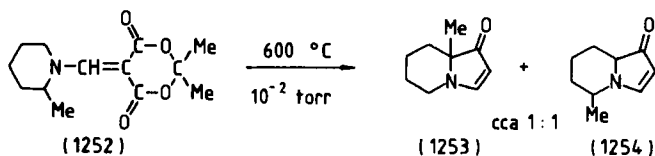
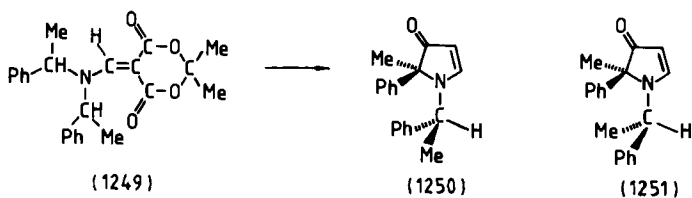
SCHEME 50

a nearly 1 : 1 mixture of the isomeric indolizinones (**1253**, **1256** and **1254**, **1257**) in 60% and 32% yields, respectively [83CC957; 88JCS(P1)863, 88JCS(P1)869, 88JCS(P2)759].

In the case of the enantiomers of isopropylidene *N*-(1-substituted tetrahydroisoquinolin-2-yl)aminomethylenemalonates (**1258**), complete loss of chirality was observed, with racemic tricyclic derivatives (**1259**) being

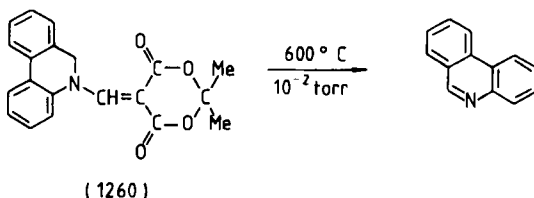


| | | | |
|---|-----|---|----|
| $R = R^1 = \text{Me}, R^2 = R^3 = (\text{CH}_2)_5$ | 56 | : | 44 |
| $R = \text{H}, R^1 = \text{Me}, R^2 = R^3 = (\text{CH}_2)_5$ | 58 | : | 42 |
| $R = R^1 = \text{H}, R^2 = R^3 = (\text{CH}_2)_5$ | 78 | : | 22 |
| $R = \text{Me}, R^1 = \text{Et}, R^2 = R^3 = (\text{CH}_2)_5$ | 40 | : | 60 |
| $R = \text{H}, R^1 = \text{Ph}, R^2 = R^3 = \text{H}$ | 100 | : | 0 |
| $R = \text{H}, R^1 = \text{Ph}, R^2 = R^3 = \text{Me}$ | 100 | : | 0 |

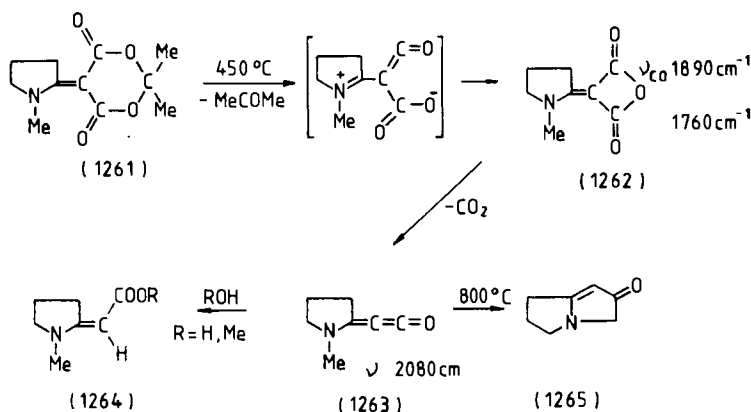


formed. In this case, a low-energy, planar configuration of a dipolar intermediate (such as **1242**) would be encouraged by conformational effects in the six-membered ring to lead to the formation of a racemic mixture [87CC138; 88JCS(P1)869].

However, the flash vacuum pyrolysis of dihydrophenanthridinylmethylenemalonate (**1260**) gave only phenanthridine in 43% yield [88JCS-(P1)863].

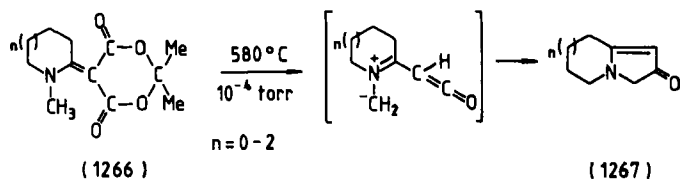


Wentrup and co-workers investigated the flash vacuum pyrolysis of isopropylidene (1-methylpyrrolidin-2-ylidene)malonate (**1261**) (86CC369) (Scheme 51). When the pyrolysis was carried out at 450°C (10^{-4} torr, contact time 10^{-3} sec), and the product was condensed on a cold finger at -196°C , (pyrrolidinylidene)malonic anhydride (**1262**) could be identified. Malonic anhydride (**1262**) in chloroform solution at -20°C lost carbon dioxide to give methyleneketene (**1263**), which was reacted with a few drops of water or methanol to yield acrylates (**1264**). Flash vacuum pyrolysis of **1261** at higher temperature (800°C) gave pyrrolopyrrolone (**1265**). The products were characterized by IR and ^{13}C -NMR data.

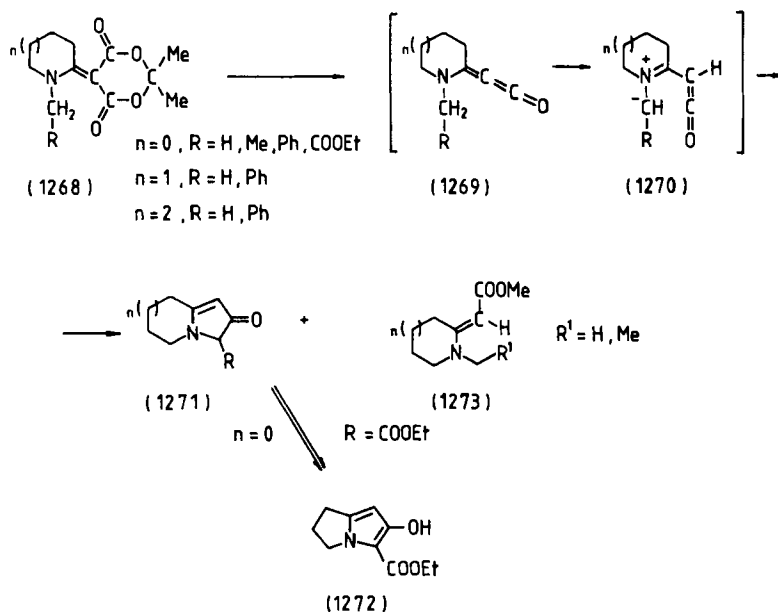


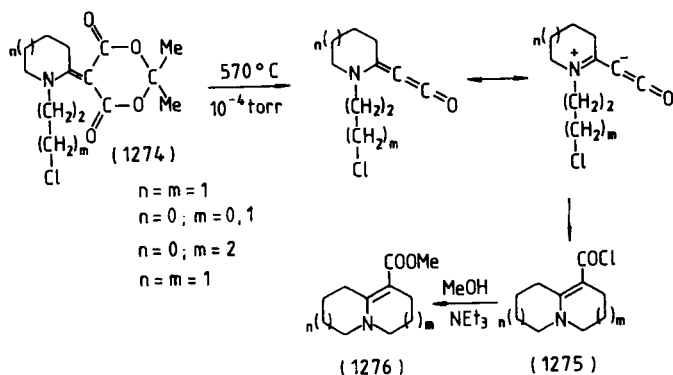
SCHEME 51

N-Methyl homologues of **1261** (**1266**, $n = 0-2$) gave bicyclic pyrrolones (**1267**, $n = 0-2$) in 73–78% yields (85TL833).



Depending on the reaction temperature (460–600°C), a mixture of bicyclo[$(n + 3)3.0$]pyrroles (**1271**) and cyclic enamino esters (**1273**) was prepared in good yield by the flash vacuum pyrolysis (10⁻⁴–10⁻⁵ torr) of isopropylidene (1-alkyl-1-azacycloalk-2-ylidene)malonates (**1268**, $R = H, Me$), when the products were condensed on a liquid nitrogen-cooled finger covered with methanol (88JOC5680). A higher temperature resulted in an increase in the percentage of bicyclic products (**1271**), and at above 600°C, only the heterocycles (**1271**) were isolated. From the 1-benzyl and 1-ethoxycarbonylmethyl derivatives (**1268**, $R = Ph, COOEt$), only bicyclic products (**1271**, $R = Ph, COOEt$) were obtained, even at a lower temperature (480°C). Bicyclic products (**1271**) were probably formed from intermediate ketenes (**1269**) through an intramolecular 1,4-hydrogen migration





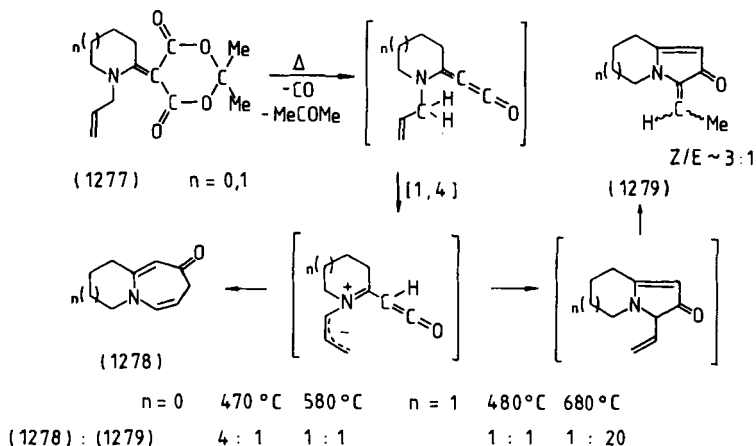
SCHEME 52

(1270), followed by a 6π electrocyclization. The ethoxycarbonyl derivative ($R = COOEt$, $n = 0$) exists in enolic tautomeric form (1272).

Dhimane *et al.* studied the flash vacuum pyrolysis of isopropylidene [1-(ω -chloroalkyl)-1-azacycloalk-2-ylidene]malonates (1274) at $570^\circ C$ and 10^{-4} torr (87TL885; 89T6161) (Scheme 52). They obtained bicyclic esters (1276) in 35–45% yields when the pyrolytic products were condensed on a cold finger at $-196^\circ C$, covered with methanol, and triethylamine was introduced at the end of the reaction. Pyrolysis of the pyrrolidine derivative (1274, $n = 0$, $m = 1$) without methanol on the cold finger afforded the bicyclic carboxylic chloride (1275, $n = 0$, $m = 1$), which was converted to ester (1276, $n = 0$, $m = 1$) by treatment with a mixture of methanol and triethylamine.

The flash vacuum pyrolysis of isopropylidene (1-allyl-1-azacycloalk-2-ylidene)malonate (1277) at 460 – $680^\circ C$ and 10^{-5} – 10^{-3} torr yielded a mixture of bicyclic azepines (1278) and pyrrolinones (1279) (85TL833) (Scheme 53). The ratio of 1278 and 1279 shifted towards the lower homologue (1279) at higher reaction temperature.

The gas-phase pyrolysis of vinylogous systems of isopropylidene aminomethylenemalonates (1280, 1287, and 1290), prepared from the appropriate enaminone or dienaminone and Meldrum's acid in pyridine, was studied by McNab *et al.* at $500^\circ C$ and 10^{-2} torr (87CC140). Flash vacuum pyrolysis of 1280 gave 1*H*-azepinones (1283) in $\sim 60\%$ yields, together with a small amount of cyclopentadienone dimer (1284). They suggested that the azepinones (1283) were formed by electrocyclization from dipolar intermediates (1282) produced from the methyleneketenes (1281) by hydrogen transfer (Scheme 54). Cycloaddition of 1282 yielded bicyclics (1285), which col-

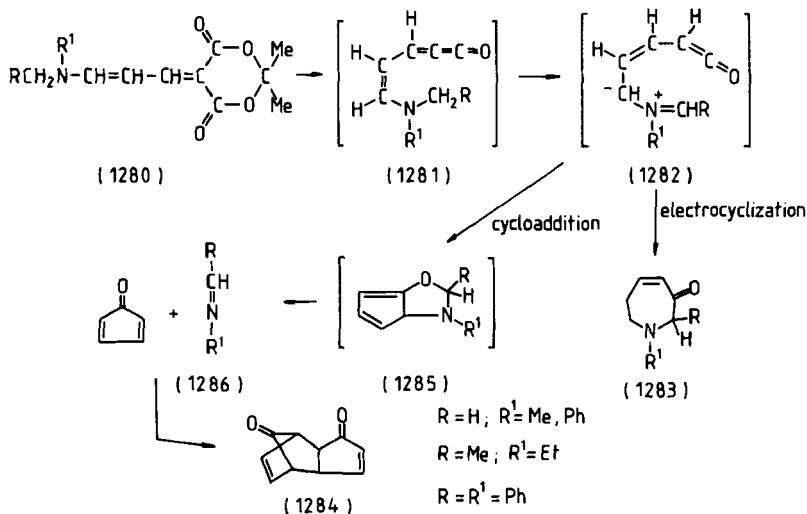


SCHEME 53

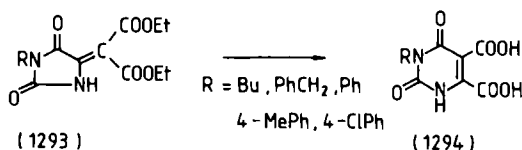
lapsed to azomethines (1286) and cyclopentadienone, which then dimerized to 1284.

N-Isopropyl-*N*-methyl derivatives (1287) afforded a mixture of 1*H*-azepinones (1288 and 1289) and 1284 (87CC140).

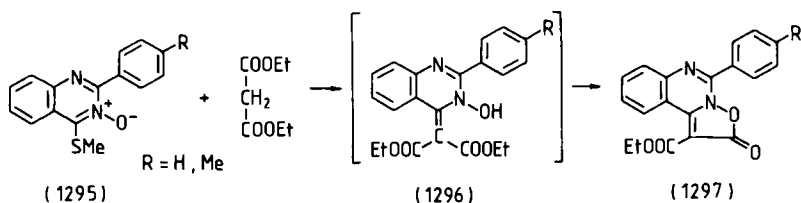
The flash vacuum pyrolysis of a higher homologue (1290) yielded benzamide, instead of the nine-membered azoninone, in 73% yield (87CC140).



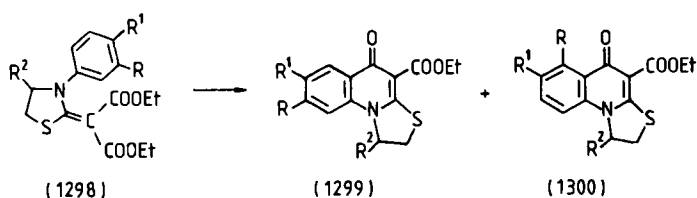
SCHEME 54



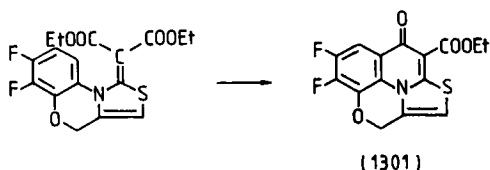
The reaction of diethyl malonate and 2-aryl-4-methylthioquinazoline-3-oxides (**1295**) in boiling acetonitrile, in the presence of potassium *tert*-butoxide for 24 hr under nitrogen, afforded isoxazolo[2,3-*c*]quinazolines (**1297**, via **1296**, in 57–61% yields (87SC1449).



Diethyl (1,3-thiazolidin-2-ylidene)malonates (**1298**) were cyclized by heating in polyphosphoric acid at 80–120°C for 1.5–3.0 hr to give thiazolo[3,2-*a*]quinolines in 43–98% yields (82EUP58392). Thiazolidinyldemalonates (**1298**, $\text{R}^1 = \text{H}$) containing a *meta*-substituted phenyl ring gave a mixture of isomeric thiazolo[3,2-*a*]quinolines (**1299** and **1300**).



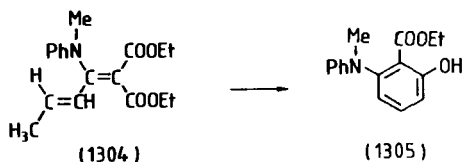
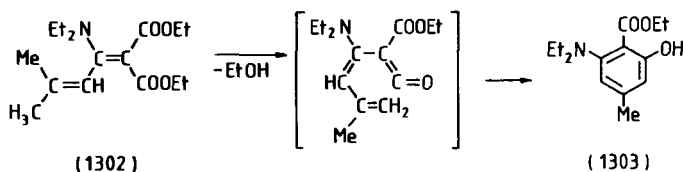
The cyclization of (thiazolo[4,3-*c*]-1,4-benzoxazin-1-ylidene)malonate in polyphosphate at 138°C for 1.5 hr gave the tetracyclic derivative (**1301**) in 61% yield [88EUP286089; 89JAP(K)117888].



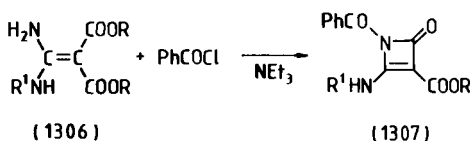
D. Further Ring Closures

The thermolysis of diethylaminomethylenemalonate (**1302**) in mesitylene at 160°C for 6 hr yielded anthranilate (**1303**), but when the reaction was carried out in heptanol, only reesterified aminomethylenemalonate was obtained (88JOC880).

Heating *N*-methyl-*N*-phenylaminomethylenemalonate (**1304**) in a distillation apparatus at 240°C for about 20 min afforded anthranilate (**1305**) in 56% yield (88JOC880).

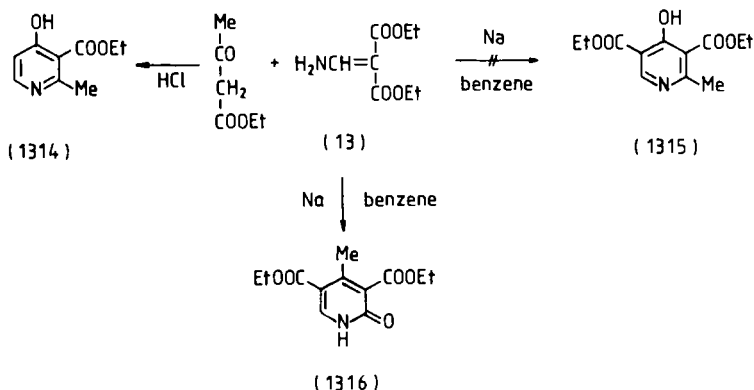


The reaction of diaminomethylenemalonate (**1306**) and benzoyl chloride in the presence of triethylamine in boiling chlorobenzene for 6 hr afforded 2-azetin-4-ones (**1307**) in 48–73% yields (77ZOR954).



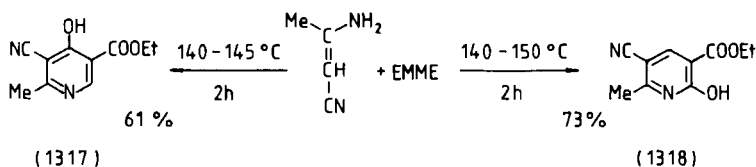
The Dieckmann cyclization of aminomethylenemalonates (**1308**) in boiling ethanol for 45 min, by the action of alkoxide, gave pyrrole-2,4-dicarboxylates (**1309**) in 24–86% yields (77HI821; 78CPB2224). Pyrrole-2,4-dicarboxylate (**1309**, R = H, R¹ = Et) was also prepared in 71% yield from **1308** (R = H, R¹ = Et) by reaction with sodium hydride in boiling benzene for 4 hr (78CPB2224). The 1-phenyl derivative (**1309**, R = Ph, R¹ = Et) was prepared in 52% yield in an exothermic reaction of **1308** (R = Ph,

that in the latter case 4-methyl-2-oxypyridine-3,5-dicarboxylate (**1316**) was formed (75JHC1245).



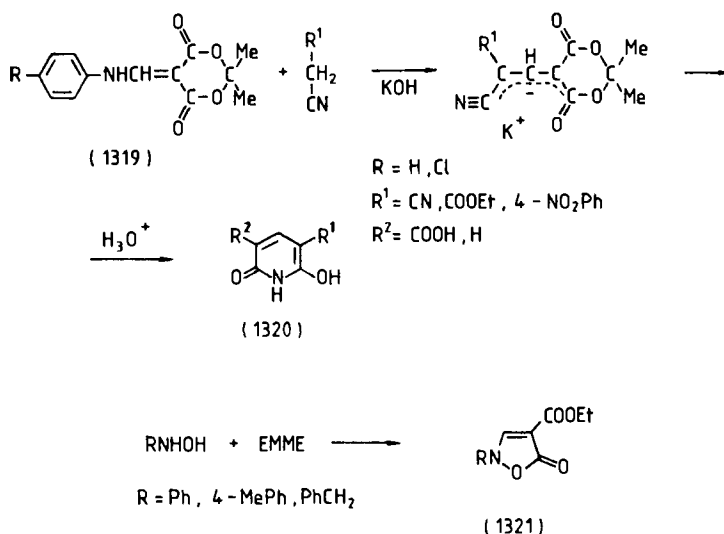
Denzel and Hans claimed that in the reaction of 3-aminocrotononitrile and EMME at 140–145°C for 2 hr, 4-hydroxy-5-cyano-6-methylpyridine-3-carboxylate (**1317**) was formed in 61% yield (73GEP2322073), but they later stated that the product was 2-hydroxy-5-cyano-6-methylpyridine-3-carboxylate (**1318**) (80USP4223142).

The reaction of ethyl 3-aminocrotonate and EMME at 100°C for 40 hr gave diethyl 2-hydroxy-6-methylpyridine-3,5-dicarboxylate in 15% yield (41CB1111).



The treatment of isopropylidene phenylaminomethylenemalonates (**1319**) with ethyl cyanoacetate or malononitrile in the presence of potassium hydroxide in DMF at 90°C afforded the potassium salts of derivatives of Meldrum's acid in 74% yields, which were converted without isolation to pyridones (**1320**) in 91% yield on the action of aqueous hydrochloric acid [78ZN(B)1550].

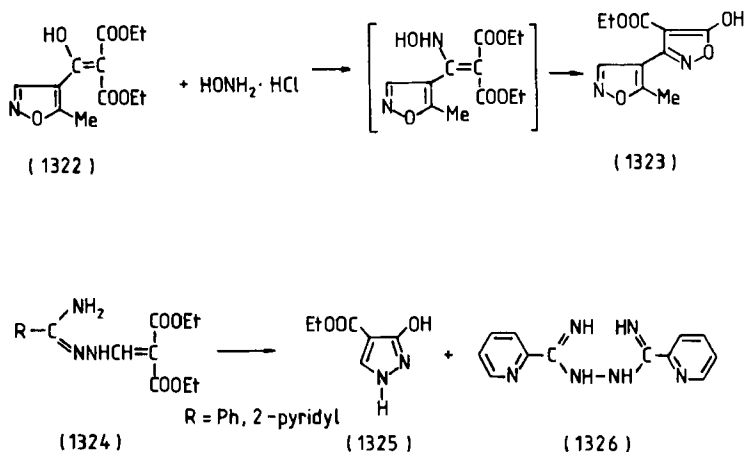
The heating of *N*-hydroxy-*N*-phenylaminomethylenemalonate (**300**) in dioxane or cyclohexane for 2 hr, or in the melt at 140°C, afforded 5-isoxazolone (**1321**, R = Ph) in 60–90% yields (24JCS1456; 63TL1365; 65T2735). 5-Isoxazolones (**1321**, R = Ph, 4-MePh, PhCH₂) were also pre-



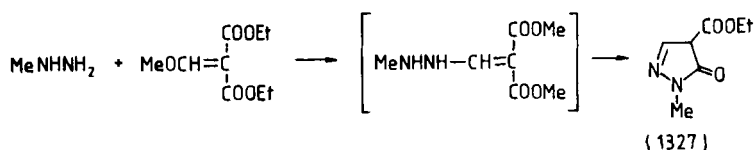
pared in 50–60% yields in the reaction of *N*-substituted hydroxylamines and EMME in boiling ethanol (74G715).

Bis(isoxazole) (1323) was prepared in 62% yield when hydroxy-(5-methylisoxazol-4-yl)methylenemalonate (1322) was reacted with hydroxylamine hydrochloride in boiling ethanol for 3 hr [88JCS(P1)1875].

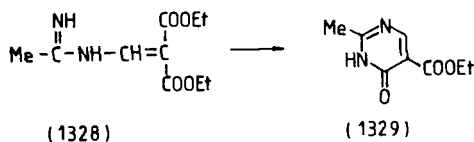
The treatment of amidrazones (1324) in ethanol with sodium ethylate at reflux temperature for 2 hr afforded pyrazolecarboxylate (1325) in 30% yields (77BCJ957). In the case of 2-pyridylamidrazone (1324, R = 2-pyridyl), the hydrazine derivative (1326) was also isolated in 8% yield.



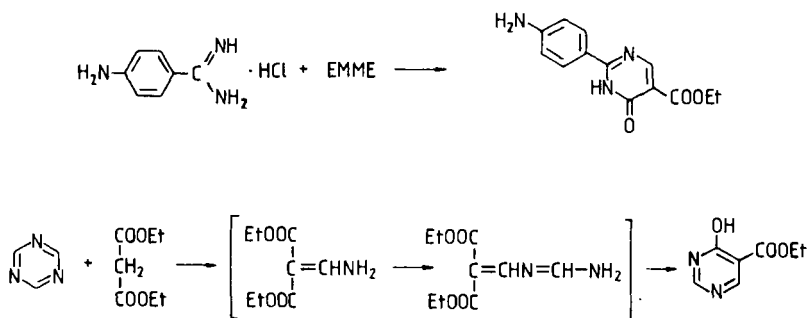
A solution of methylhydrazine in methanol was added dropwise to a solution of dimethyl methoxymethylenemalonate in methanol. The initial reaction was exothermic, and the rate of addition was controlled to achieve reflux. The reaction mixture was kept boiling for an additional 4 hr to give pyrazolecarboxylate (**1327**) in 81% yield (88JOC810). Arylhydrazonomethylenemalonates gave 1-aryl-2-pyrazolin-5-ones in boiling aqueous sodium hydroxide for 12 hr (87GEP3617554).



The ring closure of the amidine derivative (**1328**) in refluxing ethanol in the presence of sodium ethylate afforded pyrimidin-4(3*H*)-one (**1329**) (59BCJ188).



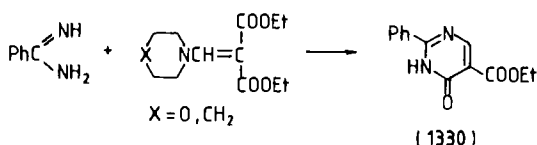
The reaction of amidines and EMME, for example in boiling ethanol in the presence of sodium ethylate, afforded pyrimidin-(3*H*)-4-one in good yields (e.g., 46JOC741; 81M15; 82USP4315933). The relevant literature is not treated in the present review. This can be found in more specialized books (62MI1; 70MI1; 85MI1). (Only a few examples are mentioned here) (Scheme 55).



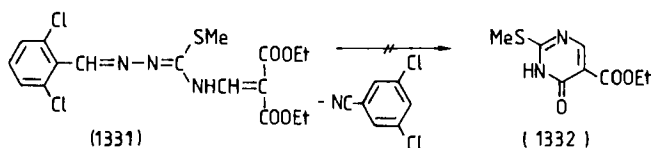
SCHEME 55

Ethyl 4-hydroxypyrimidine-5-carboxylate was obtained in 90% yield in the reaction of 1,3,5-triazine and diethyl malonate in the presence of diethylamine in ethanol for 14 days (77AP353).

The cyclocondensation of benzamidine and morpholino- or piperidino-methylenemalonates in boiling ethanol for 2 hr yielded ethyl 2-phenylpyrimidine-5-carboxylate (**1330**) (64JMC68).

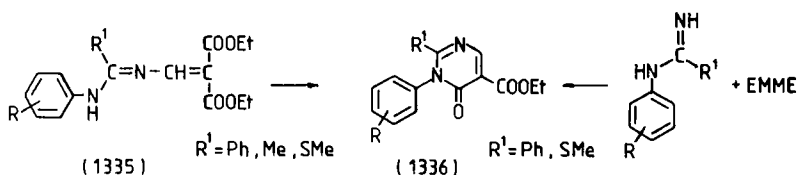
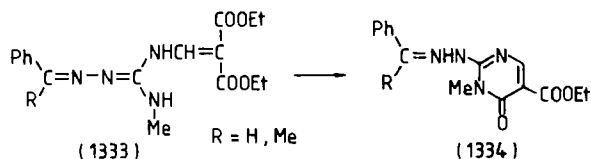


The heating of aminomethylenemalonate (**1331**) in pyridine at 160°C for 4 hr did not give 2-methylthiopyrimidin-(3*H*)-4-one (**1332**) (81JOC3956).



The cyclization of aminomethylenemalonates (**1333**) in boiling benzene for 1 hr afforded 4-(3*H*)-oxypyrimidine-3-carboxylates (**1334**) in 80–81% yields (88CPB1963).

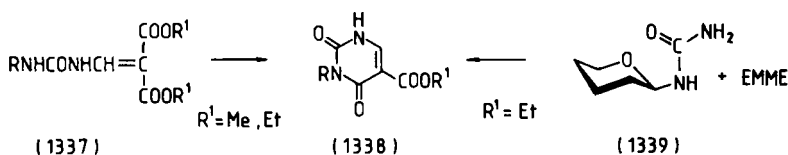
4-Oxypyrimidine-5-carboxylates (**1336**) were prepared in 50–82% yields by the cyclization of aminomethylenemalonates (**1335**) in diphenyl ether at 225°C for 1.25–75 hr, or in 38–71% yields in the reaction of *N*-arylamidines and EMME at 140°C for 18–20 hr [82IJC(B)228].



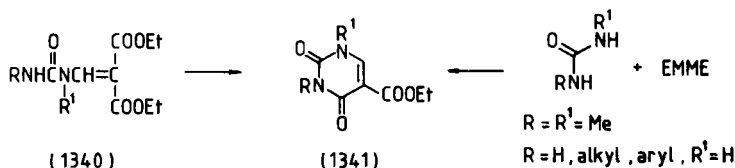
Dialkyl *N*-(aminocarbonyl)aminomethylenemalonates (**1337**, $R = H$) were treated with aqueous potassium hydroxide at room temperature. The pH of the reaction mixtures was then adjusted to 2 with hydrochloric acid, and the mixtures were heated at 80°C to give 2,4-dioxotetrahydropyrimidine-5-carboxylates (**1338**, $R = H$) in 90% yields [80JAP(K)104271]. When the cyclizations were carried out in boiling methanol in the presence of sodium methylate for 10 min, compounds **1338** ($R = H$) were prepared in 74–84% yields (81CPB3181).

The cyclization of dimethyl *N*-(methylaminocarbonyl)aminomethylenemalonate (**1337**, $R = R^1 = Me$) in boiling methanol in the presence of sodium methylate afforded 3-methyl-2,4-dioxotetrahydropyrimidine-5-carboxylate (**1338**, $R = R^1 = Me$) in 62% yield (77GEP2714392).

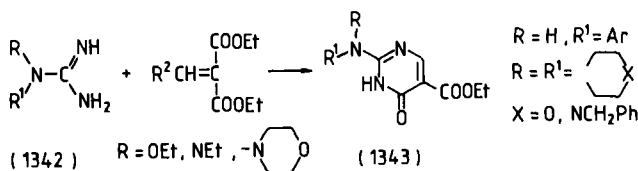
The reaction of tetrahydropyranylurea (**1339**) and EMME in ethanol in the presence of sodium ethylate at ambient temperature for 7 days gave the sodium salt of 2,4-dioxotetrahydropyrimidine-5-carboxylate (**1338**, $R = \text{tetrahydropyranyl}$, $R^1 = Et$) in 40% yield. When the reaction was performed at 40°C, partial hydrolysis of the ester group occurred, while at reflux temperature the acid (**1338**, $R^1 = H$) was obtained (80H769).



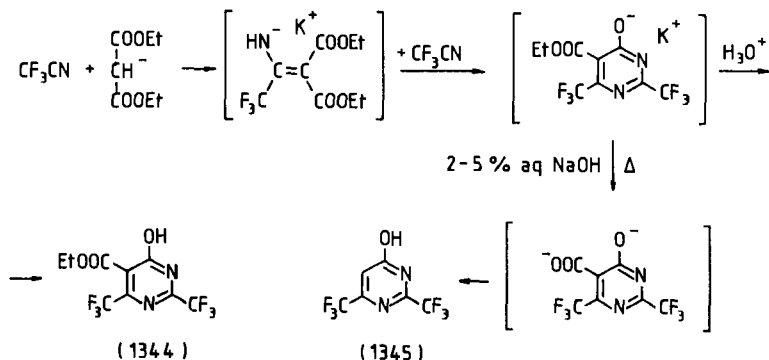
2,4-Dioxotetrahydropyrimidine-5-carboxylates (**1341**) were prepared in 50–72% yields, by the cyclization of *N*-(aminocarbonyl)aminomethylenemalonates (**1340**) in alcohol by the action of sodium alcoholate, or in 48–97% yields in the reaction of *N*-substituted urea and EMME in ethanol in the presence of sodium ethylate at room temperature for several days. Compounds **1341** were also prepared in 41 and 62% yields, respectively, in the reactions of *N*-methyl- and *N,N'*-dimethylurea and EMME in the melt at 120°C for 24 hr (52JA4267).



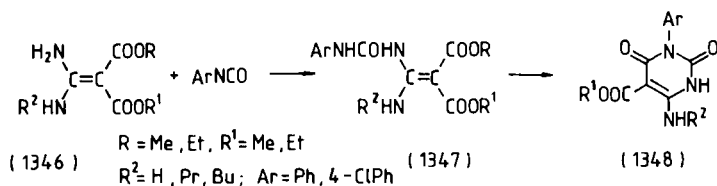
The cyclocondensation of guanidine derivatives (**1342**) and EMME [e.g., 81ZC101; 86JAP(K)87672, 86JAP(K)91176; 87USP4666915] or diethyl 4-morpholinyl- or *N,N*-diethylaminomethylenemalonates (87USP4666915) by heating in a solvent (e.g., ethanol, dioxane, dimethylformamide, water), in the presence of a base (e.g., sodium ethylate, potassium carbonate) gave 2-amino-4-(3*H*)-oxypyrimidine-5-carboxylates (**1343**) in 58–82% yields.



An excess of trifluoroacetonitrile was gradually added with vigorous stirring at 60°C to the potassium salt of diethyl malonate, prepared from diethyl malonate and potassium *tert*-butoxide, under nitrogen in THF. The reaction mixture was then allowed to cool to ambient temperature and was diluted with water. When the mixture was extracted again with diethyl ether, and the aqueous layer was acidified with concentrated hydrochloric acid and extracted again with diethyl ether, the pyrimidine-5-carboxylate (**1344**) was obtained in 88% yield after evaporation of the dried ethereal solution. In another case, when the aqueous reaction mixture was extracted with methylene chloride, the aqueous layer was treated with 50% aqueous sodium hydroxide, the mixture was refluxed for 2 hr then cooled and acidified with concentrated hydrochloric acid, and the reaction mixture was heated again while a stream of hydrogen chloride was slowly passed in, 2,6-bis(trifluoromethyl)-4-hydroxypyrimidine (**1345**) was obtained in 72% yield after the work-up process (89JHC7).

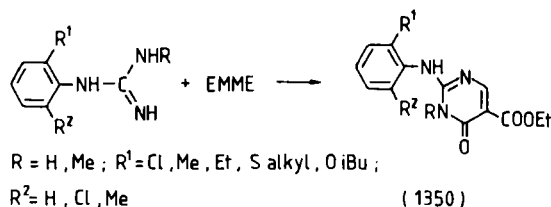
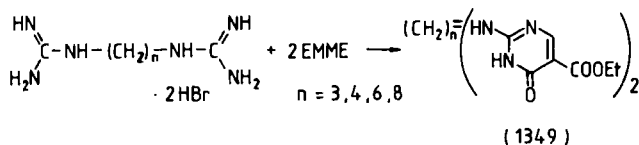


(Bisamino)methylenemalonates (**1346**, $R = R^1$) were reacted with aryl isocyanates in boiling chlorobenzene for 3–4 hr to give pyrimidine-5-carboxylates (**1348**) in 28–52% yields (76ZOR2253). When ethyl, methyl amino(butylamino)methylenemalonate (**1346**, $R = Et$, $R^1 = Me$, $R^2 = Bu$) was reacted with phenyl isocyanate, the methyl ester (**1348**, $R^1 = Me$, $R^2 = Bu$) was obtained in 38% yield. In the case of (bisamino)methylene-malonate (**1346**, $R = R^1 = Et$, $R^2 = H$) and phenyl isocyanate, malonate **1347** ($R = R^1 = Et$, $R^2 = H$) was also isolated, which could be cyclized to the corresponding pyrimidine (**1348**, $R^1 = Et$, $R^2 = H$).

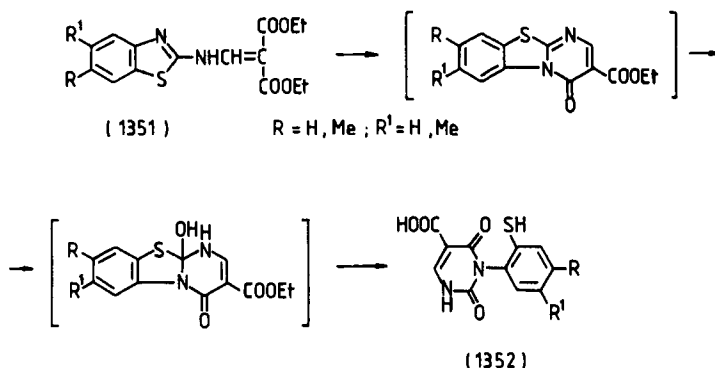


Bis(guanidinium)bromides were reacted with EMME in boiling ethanol in the presence of sodium ethoxide for 24 hr to give bis(pyrimidines) (**1349**) in 15–45% yields (84JHC209).

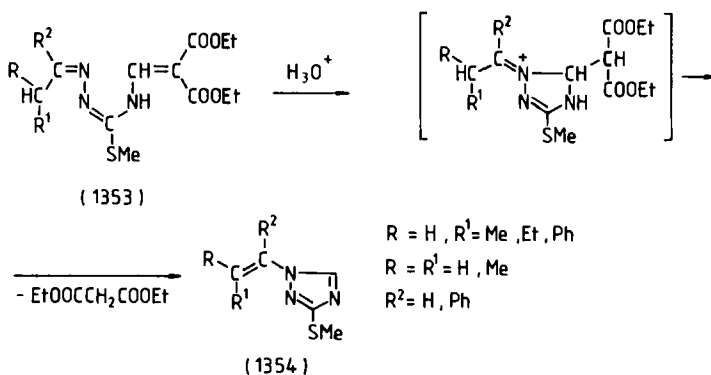
The cyclocondensation of phenylguanidines and EMME in boiling ethanol for 4 hr afforded 2-anilinopyrimidine-5-carboxylates (**1350**) in 32–77% yields (89CPB1780).



Boiling aqueous ethanolic solutions of 2-benzothiazolylaminomethylenemalonates (**1351**) in the presence of sodium hydroxide for 30 min gave 1-substituted 2,4-dioxypyrimidine-5-carboxylic acids (**1352**) in 52–70% yields (79GEP2810863, 79SAP1053).

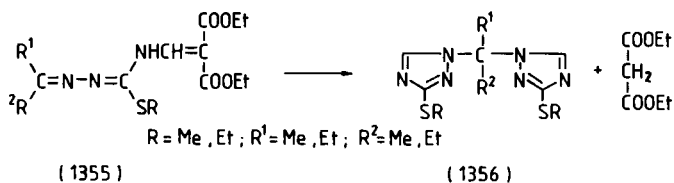


The heating of aminomethylenemalonates (**1353**, $R^2 = \text{Ph}$) in acetic acid at 90°C for 1.5–3.0 hr gave 1,2,4-triazoles (**1354**, $R^2 = \text{Ph}$) in 59–82% yields, together with diethyl malonate (85JOC5513). When compound **1353** ($R = R^1 = \text{H}$, $R^2 = \text{Ph}$) was refluxed in formic acid for 2.5 hr, 1,2,4-triazole (**1354**, $R = R^1 = \text{H}$, $R^2 = \text{Ph}$) was obtained in only 43% yield.



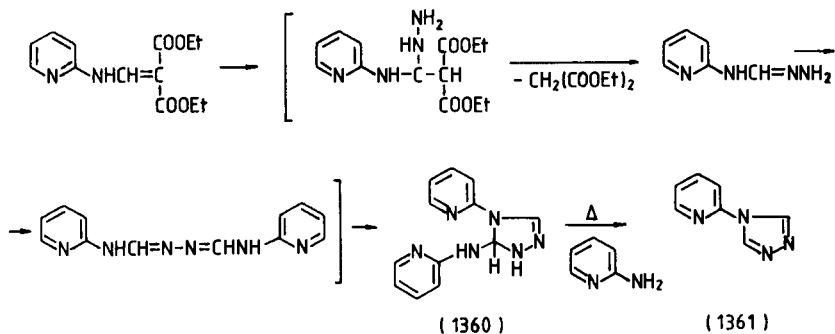
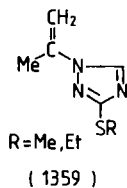
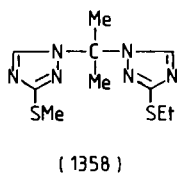
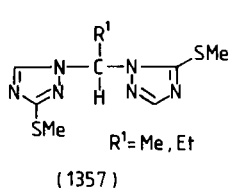
The acetaldehyde derivative (**1353**, $R-R^2 = \text{H}$) was heated in boiling toluene in the presence of trichloroacetic acid for 30 min to afford 1,2,4-triazole (**1354**, $R-R^2 = \text{H}$) in 2% yield (85JOC5513).

The heating of solutions of aminomethylenemalonates (**1355**, $R = \text{Me}$, Et ; $R^1 = \text{Me}$, $R^2 = \text{Me}$, $i\text{Pr}$) in aqueous acetic acid at 70°C for 2 hr gave bis(1,2,4-triazol-1-yl)alkanes (**1356**, $R = \text{Me}$, Et , $R^1 = \text{Me}$, $R^2 = \text{Me}$, $i\text{Pr}$) in 33–60% yields, after the work-up process [88JCS(P1)1897]. From the derivative of **1355** ($R = \text{Me}$, $R^1 = \text{Me}$, $R^2 = \text{Et}$), compound **1356** ($R = \text{Me}$, $R^1 = \text{Me}$, $R^2 = \text{Et}$) was obtained in 30% yield in 93% aqueous



acetic acid at 70°C for 2 hr, but 3-methylthio-1*H*-1,2,4-triazole (90%) was the product when 63% aqueous acetic acid was applied.

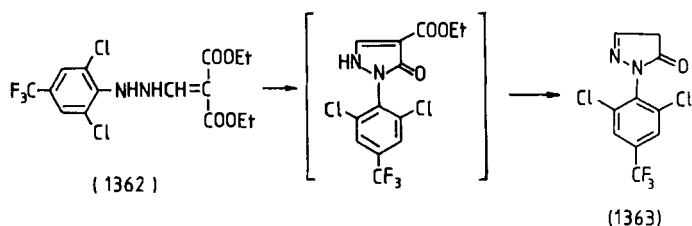
The similar reactions of aldehyde derivatives (**1355**, R = Me, R¹ = Me, Et, R² = H) in 63% aqueous acetic acid at 70°C for 2 hr gave two types of bis(triazoles) (**1356**, R = Me, R¹ = Me, Et, R² = H, and **1357**, R¹ = Me, Et) in 47–54% and 8–11% yields, respectively [88JCS(P1)1897]. When a mixture of aminomethylenemalonates (**1355**, R = Me, Et, R¹ = R² = Me) was heated in 93% aqueous acetic acid at 70°C for 2 hr, a mixture of two symmetric bis(1,2,4-triazoles) (**1356**, R = Me, Et, R¹ = R² = Me), an unsymmetric bis(1,2,4-triazoles) (**1358**), and 1-isopropenyl-1*H*-1,2,4-triazoles (**1359**, R = Me and Et) was isolated from the reaction mixture [88JCS(P1)1897].



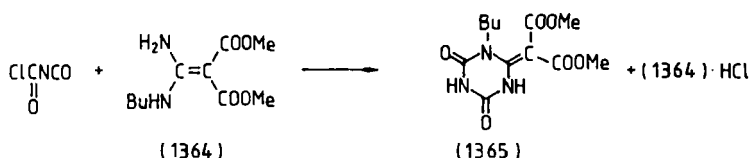
The reaction of diethyl 2-pyridylaminomethylenemalonate and hydrazine at room temperature gave 4-(2-pyridyl)-5-(2-pyridyl)amino-1,2,4-triazoline (**1360**) and diethyl malonate, while in boiling ethanol it afforded

4-(2-pyridyl)-1,2,4-triazole (**1361**). Compound **1360** could be transformed into **1361** by heating or by treatment with strong base. 4-(3-Pyridyl)- and 4-(2-pyrazinyl)-1,2,4-triazole were prepared similarly. Phenylaminomethylenemalonate did not react with hydrazine hydrate in ethanol at ambient temperature, but under reflux, 5-hydroxypyrazole-4-carboxylate (**14**, R = H) was obtained. Pyrazolecarboxylate (**14**, R = H) was also prepared from *N*-(4-ethylphenyl)aminomethylenemalonate and 1-piperazinylmethylenemalonate under similar reaction conditions (70T3069).

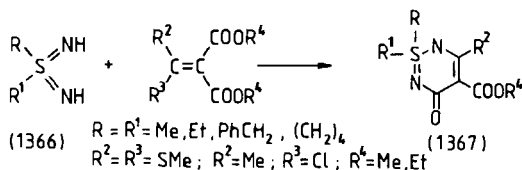
Pyrazole (**1363**) was prepared in 67% yield when hydrazinomethylenemalonate (**1362**) was heated in 3% aqueous sodium hydroxide solution at 97–98°C for 48 hr (88GEP3728278).



The reaction of dimethyl amino(butylamino)methylenemalonate (**1364**) and *N*-(chlorocarbonyl)isocyanate in benzene afforded (1,3,5-triazin-2-ylidene)malonate (**1365**) in 52% yield and the hydrochloride salt of the starting material (**1364** × HCl) (76ZOR2253).

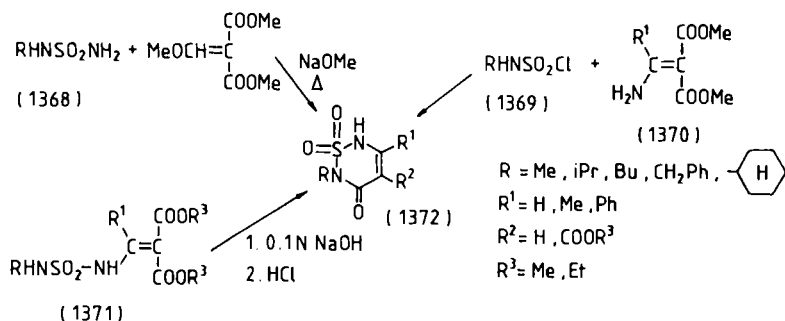


The reaction of *S,S*-dialkylsulfurdiimides (**1366**) with dimethyl bis(methylmercapto)methylenemalonate (R² = R³ = SMe, R⁴ = Me) at 65°C for 24 hr, or with diethyl (1-chloroethylidene)malonate (R² = Me, R³ = Cl,

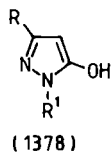
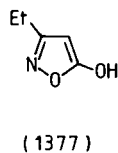
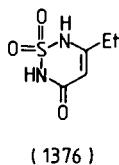
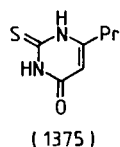
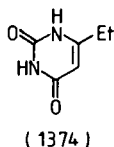
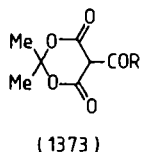


$R^4 = \text{Et}$) in methylene chloride in the presence of triethylamine, afforded 5-methylthio- and 5-methyl-3-oxo-3*H*-1 λ ⁶, 2,6-thiadiazine-4-carboxylates (**1367**, $R^2 = \text{MeS}$ and Me), respectively, in 13–35% yields (86CB1745).

The cyclization of sulfamidoaminomethylenemalonate (**1371**, $R = R^1 = \text{H}$, $R^3 = \text{Et}$) in ethanol by the action of sodium ethylate at ambient



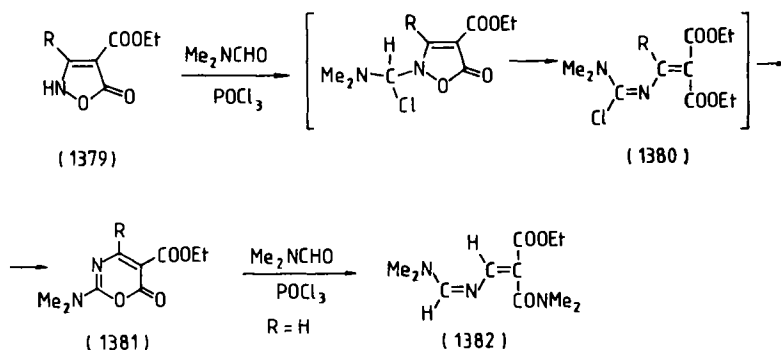
temperature for 12 hr gave 1,2,6-thiadiazine-4-carboxylate (**1372**, $R = R^1 = \text{H}$, $R^2 = \text{COOEt}$) (78JHC253). 3-Unsubstituted 1,2,6-thiadiazine-4-carboxylates (**1372**, $R = \text{H}$, $R^1 = \text{H}$, $R^2 = \text{COOMe}$) were prepared in 25–41% yields in the reactions of substituted sulfamides (**1368**) and dimethyl methoxymethylenemalonate in boiling methanol in the presence of sodium methoxide for 8 hr (79LA950). 3-Substituted 1,2,6-thiadiazines (**1372**, $R \neq \text{H}$, $R^1 \neq \text{H}$, $R^2 = \text{H}$) were obtained in 29–96% yields when aminomethylenemalonates (**1370**, $R^1 = \text{Me}, \text{Ph}$) were first reacted with alkylsulfamoyl chlorides (**1369**, $R = i\text{Pr}, \text{Bu}, \text{cyclohexyl}$) in toluene in the presence of triethylamine, followed by evaporation to give residues which were treated with 1 N sodium hydroxide solution for 6 days. The treat-



ment of 1-(sulfamido)ethylidenemalonates (**1371**, $R = iPr$, cyclohexyl, $R^1 = R^3 = Me$) with 0.1 N sodium hydroxide solution for 6 days at ambient temperature also afforded 3-substituted 1,2,6-thiadiazines (**1372**, $R = iPr$, cyclohexyl, $R^1 = R^2 = Me$) (79LA950).

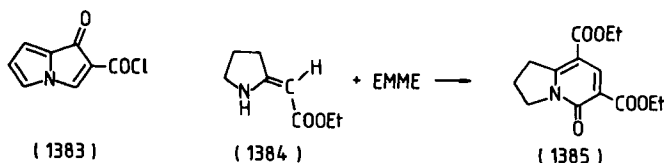
The reactions of 5-acyl-2,2-dimethyl-4,6-dioxo-1,3-dioxanes (**1373**) with urea, thiourea, sulfamide, hydroxylamine, or 1-substituted hydrazines gave monocyclic six- and five-membered heterocycles (**1374–1378**) in good yields [79JAP(K)106466].

The reactions of isoxazolin-5-ones (**1379**) with 1 mol of phosphoryl chloride and DMF in boiling chloroform for 1.5 hr afforded 1,3-oxazin-6-ones (**1381**) in 69–74% yields via aminomethylenemalonate derivatives (**1380**) (87JOC3426). If 2 mols of Vilsmeier–Haack reagent were used in boiling carbon tetrachloride for 2 hr, then **1381** ($R = H$) and the aminomethylenemalonamate derivative (**1382**) were obtained in 8% and 76% yields, respectively, from **1379** ($R = H$).

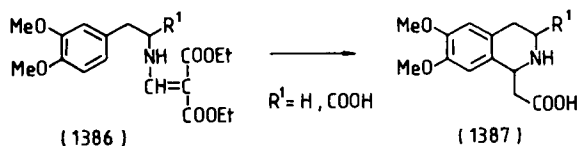


The treatment of 1-pyrrolylmethylenemalonic acid (**118**) with phosphorus pentachloride in methylenechloride at ambient temperature gave 1-oxo-1*H*-pyrrolizine-2-carbonyl chloride (**1383**) in 42% yield (82CB706).

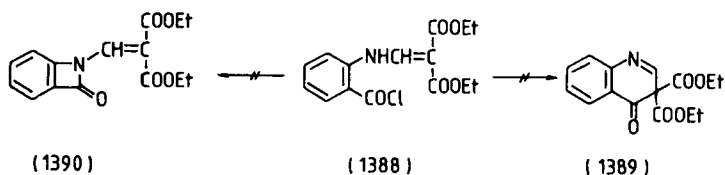
(Pyrrolidin-2-ylidene)acetate (**1384**) reacted with EMME in benzene on the carbon atom instead of the nitrogen. The condensation was followed by cyclization to give tetrahydroindolizinone (**1385**) in 60% yield (83H1099).



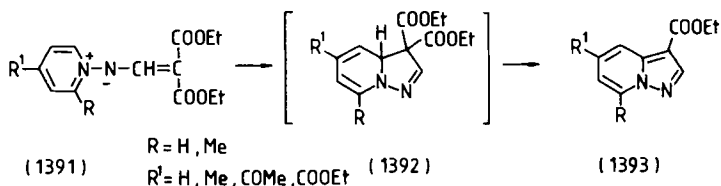
The heating of [2-(3,4-dimethoxyphenyl)ethylamino]methylenemalonates (**1386**) in 24% aqueous hydrochloric acid gave tetrahydroisoquinoline-1-acetic acid hydrochlorides (**1387**) in good yields (56JOC336; 76IJC784).



From *N*-(2-chlorocarbonylphenyl)aminomethylenemalonate (**1388**), neither the dihydroquinoline (**1389**) nor the benzazetidone derivative (**1390**) could be obtained (73IJC1332).

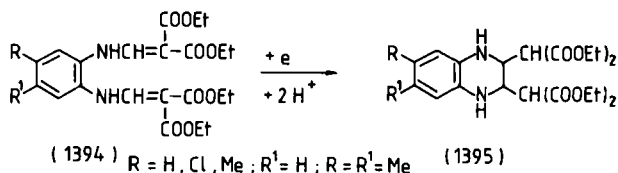


The ring closure of ylides (**1391**) by heating in boiling xylene for 1.5 hr afforded pyrazolo[1,5-*a*]pyridine-3-carboxylates (**1393**) in 14–25% yields [73JCS(P1)2580]. The pyrazolo[1,5-*a*]pyridines (**1393**) were probably formed from the intermediate dihydropyrazolo[1,5-*a*]pyridines (**1392**) by the formal elimination of ethyl formate.

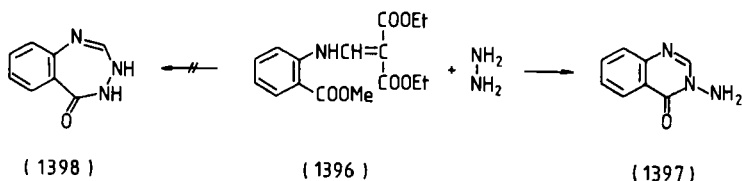


The electrochemical cyclization of bis(aminomethylenemalonates) (**1394**) in acetonitrile containing 5% water and tetraethylammonium perchlorate afforded tetrahydroquinoxalines (**1395**) in 90–96% yields (81ZC286).

Kornet proved that the product obtained in the reaction of *N*-(2-



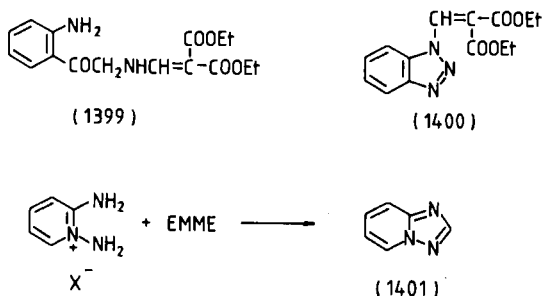
methoxycarbonylphenyl)aminomethylenemalonate (**1396**) and hydrazine hydrate in ethanol was 3-amino-4-quinazoline (**1397**) (73JPS834) and not 1,3,4-benzotriazepine (**1398**), as reported earlier (69CJC489).



Sardesai and Sunthakar studied the cyclization of diethyl *N*-(2-aminophenyl)aminomethylenemalonate (**162**, R = H) (57MI2; 59MI1). No cyclization occurred in refluxing xylene in the presence or absence of a catalyst (*p*-toluenesulfonic acid or sodium hydroxide), or in acetic anhydride, or in a mixture of acetic anhydride and concentrated sulfuric acid. Benzimidazole and benzimidazolone were obtained in 20% and 66% yields, respectively, when **162** (R = H) was distilled *in vacuo*. Benzimidazolone was the product when **162** (R = H) was heated in boiling diphenyl ether. *o*-Phenylenediamine was reacted with diethyl acetylmalonate at 140°C for 4 hr to give 2-methylbenzimidazole and diethyl malonate (85S555).

[(2-Aminophenyl)carbonylmethylamino]methylenemalonate (**1399**) could not be cyclized under a wide variety of conditions [76JCS(P1)1331].

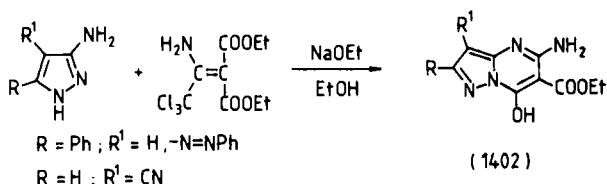
The diazotization of diethyl *N*-(2-aminophenyl)aminomethylenemalo-



nate (**162**, R = H) with sodium nitrite in aqueous hydrochloric acid at -5 to 0°C for 30 min gave 1-benzotriazolylmethylenemalonate (**1400**) (73IJC1332).

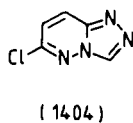
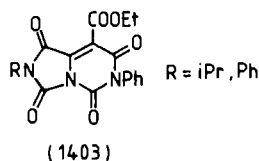
The reaction of 1,2-diaminopyridinium salt and EMME in ethanol in the presence of potassium carbonate afforded 1,2,4-triazolo[1,5-*a*]pyridine (**1401**) in 67% yield (75YZ1497).

Pyrazolo[1,5-*a*]pyrimidine-6-carboxylates (**1402**) were prepared in 70% yields in the reaction of 3-aminopyrazoles and diethyl amino(trichloromethyl)methylenemalonate in boiling ethanol in the presence of sodium ethoxide for 6 hr (78JPR533).

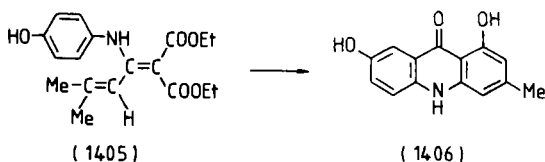


The cyclocondensation of (imidazolidin-2-ylidene)malonates (**1293**, R = *i*Pr, Ph) and phenyl isocyanate in boiling methylene chloride in the presence of tetramethylammonium fluoride and triethylamine for 10.5 hr gave imidazo[1,5-*c*]pyrimidines (**1403**) in low yields [83JAP(K)88383].

Triazolo[4,3-*b*]pyridazine (**1404**) was prepared in 75% yield, in the cyclocondensation of 3-chloro-6-hydrazinopyridazine and EMME in boiling acetonitrile for 3 hr, or in 94% yield in the cyclization of hydrazinomethylenemalonate (**195**) in boiling acetonitrile for 4 hr (80JHC1527).

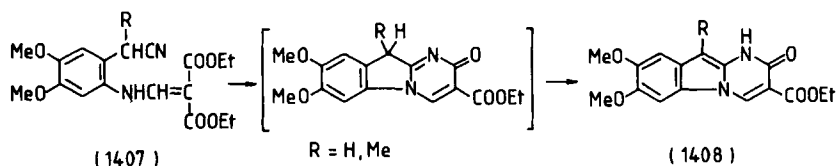


The heating of phenylaminomethylenemalonate (**1405**) at 240°C for about 30–60 min in vacuum (20–40 mm Hg) gave acridone (**1406**) in 38% yield (88JOC880).

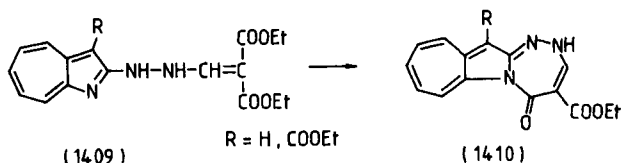


Pyrimido[1,2-*a*]indolecarboxylates (**1408**) were prepared by the cyclization of phenylaminomethylenemalonates (**1407**) in boiling ethanol in the presence of 1 mol. equiv. of sodium ethylate for 3 hr (68JOC1345; 70USP3546225).

Perimidine was formed in the strongly exothermic reaction of 1,8-diaminonaphthalene and EMME (67N115).



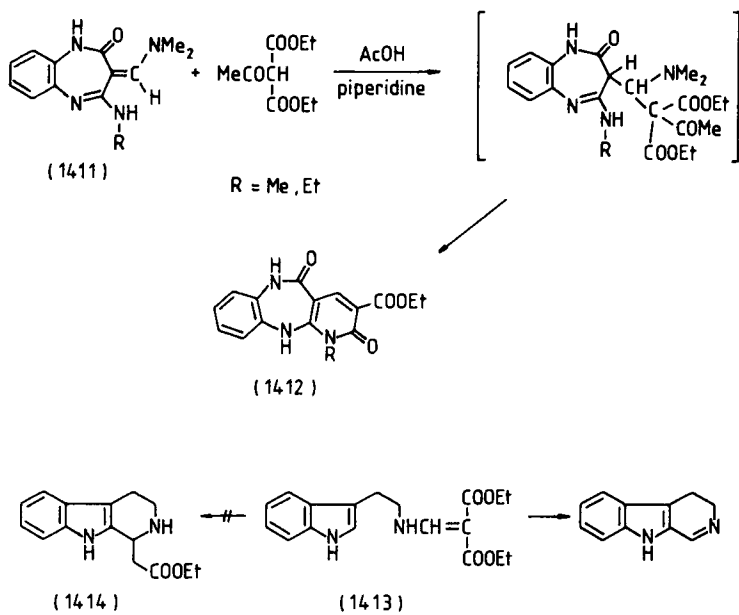
The cyclization of (1-azaazulen-2-yl)hydrazinomethylenemalonates (**1409**) in boiling *tert*-butylbenzene for 30–40 min afforded 1,2,5a-triaza-cyclohept[*a*]azulen-5-ones (**1410**) in 74–93% yields (88BCJ1440). Whereas the methyl derivative of **1409** ($\text{R} = \text{Me}$) could be cyclized in 56% yield in chloroform by treatment with silica gel at room temperature for 7 days, the ethoxycarbonyl derivative (**1409**, $\text{R} = \text{COOEt}$) could not.



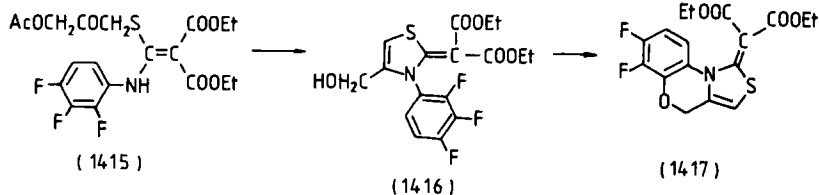
In the cyclocondensation of diethyl acetylmalonate and 4-alkylamino-1,5-benzodiazepines (**1411**) in benzene in the presence of acetic acid and piperidine, the addition of acetylmalonate at the side-chain double bond of **1411** took place first. The amino group at position 4 was involved only in the second step of the reaction sequence to give tricyclic derivatives (**1412**) in 49–77% yields (85FES391).

Groves and Swan tried unsuccessfully to cyclize *N*-2-(indol-3-yl)ethyl aminomethylenemalonate (**1413**) to tetrahydro- β -carboline-1-acetate (**1414**) by the action of an acid or base. Instead of cyclization, hydrolysis of **1413** occurred to yield tryptamine (52JCS650). Later, Maclaren obtained 3,4-dihydro- β -carboline when he treated **1413** with trifluoroacetic acid or boron trifluoride (87AJC1617).

Diethyl (2,3,4-trifluorophenylamino)(3-acetoxy-2-oxopropylthio)methylenemalonate (**1415**) was stirred in concentrated sulfuric acid at room

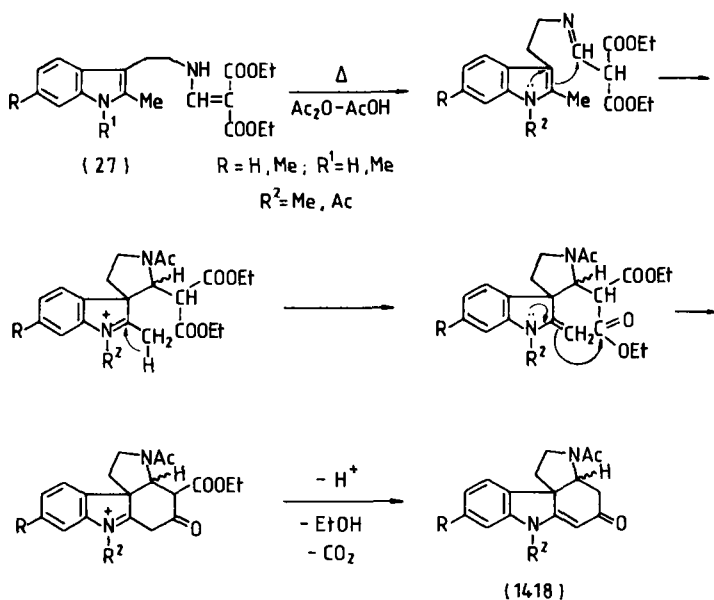


temperature for 30 min. After work-up, diethyl 3-(2,3,4-trifluorophenyl)-4-hydroxymethyl-2-thiazolidene malonate (**1416**) was obtained in 67% yield (88EUP286089). When a solution of 2-thiazolidenemalonate (**1416**) in dioxane was stirred in the presence of sodium hydride at room temperature for 20 min and then under reflux for 10 min, diethyl(6,7-difluorothiazolo[4,3-c]-1,4-benzoxazin-1-ylidene)malonate (**1417**) was prepared in 74% yield.



[2-(Indolin-3-yl)ethyl]aminomethylenemalonates (**27**) were treated with a 3 : 2 mixture of acetic anhydride and acetic acid at reflux for 72 hr to give aspidosperma alkaloids (**1418**) in 45–92% yields, as a mixture of epimers (Scheme 56) (77H1699, 77MI3; 78CC943; 79MI1).

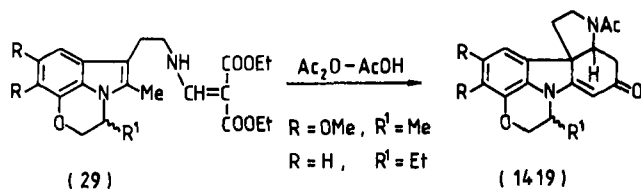
The cyclization of aminomethylenemalonates (**29**) under similar condi-

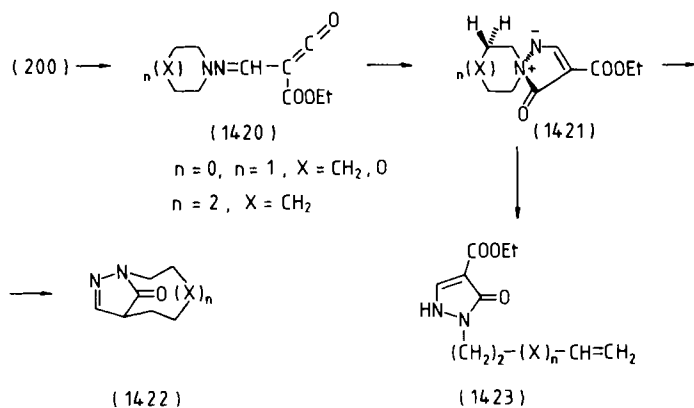


SCHEME 56

tions for 70–96 hr gave pentacyclic derivatives (**1419**) in 30–40% yields [85TL1769; 87JCS(P1)2079, 87T191].

The flow pyrolysis of aminomethylenemalonates (**200**) at relatively low temperature (325–360°C) under reduced pressure (20 torr) gave spirocyclic pyrazolium ylides (**1421**) and 1,4-bridged pyrazolin-5-ones (**1422**) in 56–74% and 0–20% yields, respectively. At higher temperature (390–420°C), the ratio of **1421** and **1422** shifted in favor of **1422**. Under the latter conditions, *N*-alkyl-5-oxo-pyrazoline-4-carboxylates (**1423**) could also be isolated in 15–38% yield from the reaction mixture of the higher homologues (**200**, $n = 1, 2$, $X = \text{CH}_2$). It was suggested that the first step of the reaction probably gave an iminoketene (**1420**) which yielded





spirocyclic derivatives (**1421**) by electrocyclization. Then both **1422** and **1423** were formed from the spiro pyrazolium ylides (**1421**), by 1,4-sigmatropic-alkyl migration and Cope or Hoffman elimination, respectively (85JOC909; 87BSF365).

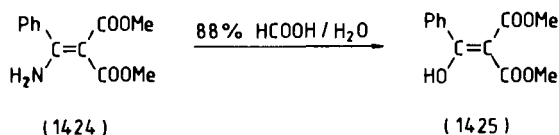
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Other Reactions of Aminomethylenemalonates

A. Reactions of Dialkyl (1-Aminoalkylidene)malonates

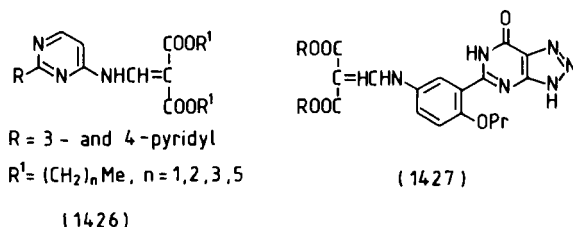
1. HYDROLYSIS, SOLVOLYSIS

Amino(phenyl)methylenemalonate (**1424**) was hydrolyzed by heating in boiling aqueous formic acid for 30 min to give hydroxy(phenyl)methylenemalonate (**1425**) (85TL2603).

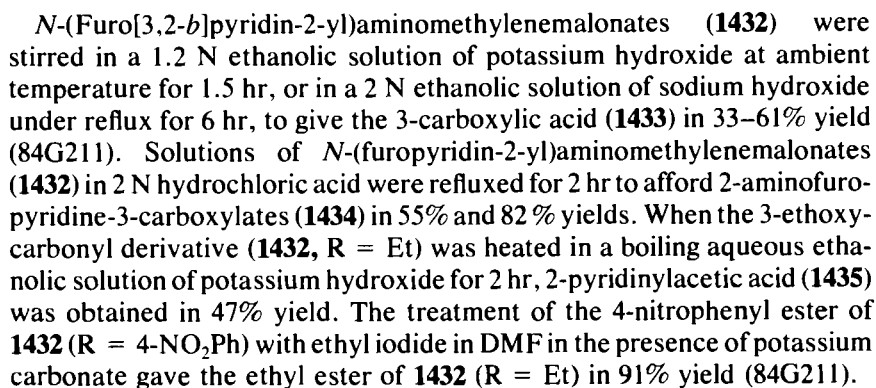
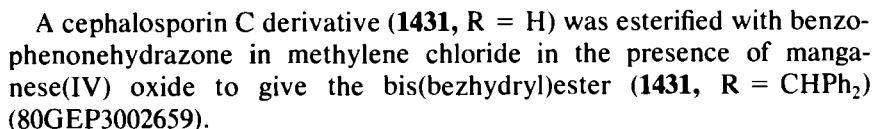
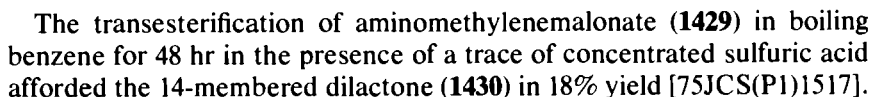


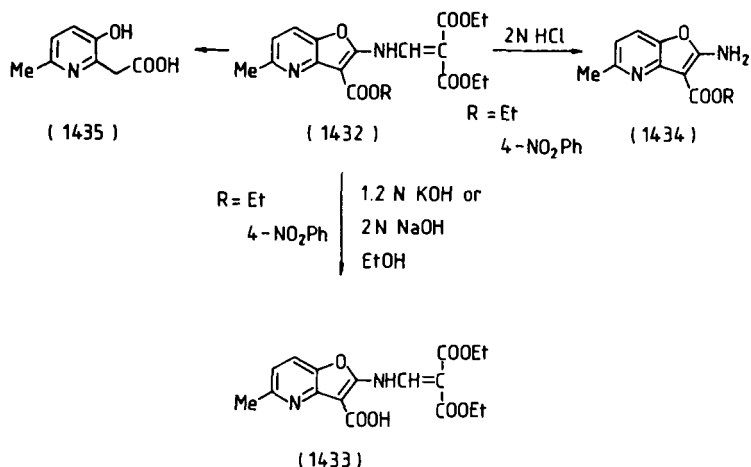
Dialkyl 4-pyrimidinylaminomethylenemalonates (**1426**, $n = 2, 3, 5$) were prepared in 70-80% yields in the base-catalyzed transesterification of diethyl 4-pyrimidinylaminomethylenemalonates (**1426**, $n = 1$) with the appropriate alkanol at ambient temperature for 120 hr in the presence of sodium hydride. Acid-catalyzed transesterification was unsuccessful (84JHC247).

The treatment of the diethyl aminomethylenemalonate derivative (**1427**, $R = \text{Et}$) in methanol in the presence of sodium methylate under reflux for 2 hr gave the dimethyl ester (**1427**, $R = \text{Me}$) in 85% yield (78GEP2747199; 82SZP627755).



Diethyl *N*-ethyl-*N*-(2,2,6,6-tetramethylpiperidin-4-yl)aminomethylenemalonate (**1428**) was transesterified with 4-hydroxy-2,2,6,6-tetramethylpiperidine in boiling xylene in the presence of sodium ethylate (88GEP3805786).

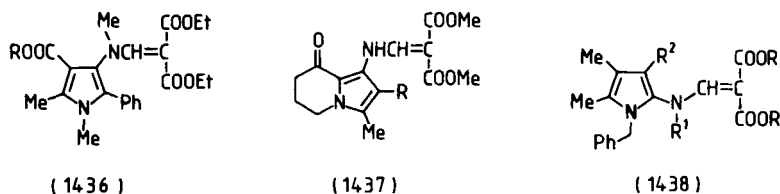




The *tert*-butoxycarbonyl group of 3-pyrrolylamino-2-methyl-5-hydroxymethylpyridine-4-carboxylic acid (**1436**, R = *t*Bu) was converted into the carboxyl group (R = H) in 91% yield by the action of methanesulfonic acid at ambient temperature for 10 min (85JHC729).

(2-*tert*-Butoxycarbonyl-1-indoliziny)aminomethylenemalonate (**1437**, R = COOtBu) was converted into 1-indolizinyaminomethylenemalonate (**1437**, R = H) in 61% yield by treatment with trifluoroacetic acid at 50°C for 45 min (85JHC817).

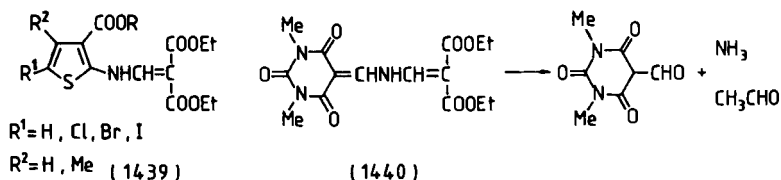
The *tert*-butyl esters of 2-pyrrolylamino-2-methyl-5-hydroxymethylpyridine-4-carboxylic acids (**1438**, R² = COOtBu) were selectively hydrolyzed with methanesulfonic acid or concentrated sulfuric acid at 0°C or at ambient temperature to afford the corresponding carboxylic acids (**1438**, R² = COOH) in 26–98% yields. The carboxylic acid (**1438**, R = Me, R¹ = H, R² = COOH) underwent facile decarboxylation upon heating at 190–200°C to give 2-pyrrolylamino-2-methyl-5-hydroxymethylpyridine-4-carboxylic acid (**1438**, R = Me, R¹ = R² = H) in 73% yield (85JHC1429).



The hydrolysis of diethyl *N*-(6-phenyl-7-hydroxy-1,8-naphthyridin-2-yl)aminomethylenemalonate in aqueous sodium hydroxide afforded 2-amino-6-phenyl-7-hydroxy-1,8-naphthyridine (69G677).

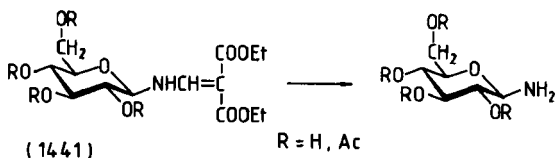
The hydrolysis of diethyl *N*-(3-alkoxycarbonyl-2-thienyl)aminomethylenemalonates (**1439**, R = Me, Et) by potassium hydroxide in ethanol yielded diethyl *N*-(3-carboxy-2-thienyl)aminomethylenemalonates (**1439**, R = H) [75GEP2435025, 75JAP(K)77393]. The treatment of the *tert*-butyl esters [**1439**, R = *t*Bu, R¹ = R² = H, Me, (CH₂)₄] with formic acid or trifluoroacetic acid at room temperature also afforded the carboxylic acid derivatives [**1439**, R = H, R¹ = R² = H, Me, (CH₂)₄] [75JAP(K)77394].

The hydrolysis of **1440** in a mixture of ethanol and 75% hydrochloric acid at reflux temperature for 24 hr gave acetaldehyde, ammonia, and 5-formyl-1,3-dimethylbarbituric acid (70AP612).



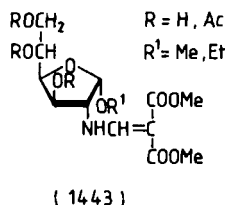
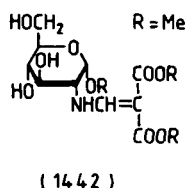
The kinetics of the hydrolysis of compound **33** was studied (86MI2).

The hydrolysis of aminomethylenemalonates (**1441**) under acidic conditions gave the corresponding amines (68MI1).



The methylenemalonate moiety of compounds **1442** and **1443** was removed by treatment with chlorine water at 0°C overnight, or by treatment with concentrated ammonium hydroxide in acetone at ambient temperature for 4 days, or by treatment with Amberlite IRA-400(HO⁻) resin in aqueous acetone at 40°C for 3 hr to give the corresponding aminoglucoside and aminofuranoside in 52–99% yields (84MI7).

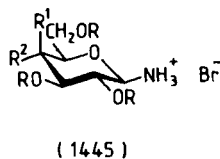
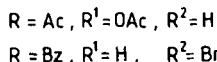
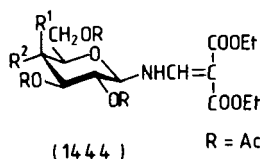
N-Deprotection of aminomethylenemalonate derivatives of 2-deoxyglucopyranose (**40**, R = H, R¹ = OMe, and R = OH, R¹ = H, R² = Ac, R³ = Et) by treatment with bromine or chlorine in chloroform afforded methyl 3,4,6-tri-*O*-acetyl-2-amino-2-deoxy-β-D-glucopyranoside hydro-



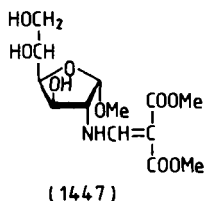
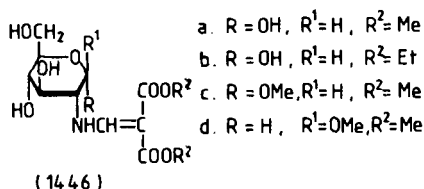
bromide and 3,4,6-tri-*O*-acetyl-2-amino-2-deoxy- α -D-glucopyranoside hydrochloride in 95% and 66% yields, respectively (88MI4).

The reactions of tetra-*O*-acylgluco- and -galactopyranosylaminomethylenemalonates (**1444**) and bromine in a mixture of chloroform and water at room temperature for 2 days gave the corresponding tetra-*O*-acylamine hydrobromides (**1445**) in 81–96% yields (86MI8).

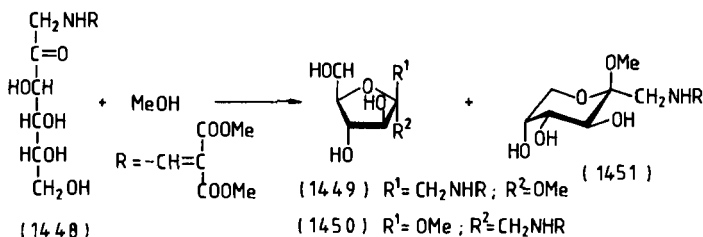
The hydrolysis of the α -D-fructofuranoside derivative with Amberlite IRA-400(HO^-) resin in aqueous acetone gave the 1-amino-1-deoxy- α -*O*-fructofuranoside in quantitative yield (86MI10).



The treatment of **1446a** with a boiling 3% solution of hydrogen chloride in methanol for 5 hr gave a mixture of **1446c** and **1446d** (in 7 : 3 ratio) and glucofuranoside (**1447**). At room temperature no reaction occurred. Methyl glycosidation of **1446a** in boiling methanol in the presence of Amberlyst-15(H^+) resin for 24 hr afforded a mixture of **1446c**, **1446d** (in 2 : 3 ratio), and **1447**. The glucofuranoside (**1447**) was converted almost quantitatively into the thermodynamically more stable glucopyranoside (**1446c**) by heating in methanolic hydrogen chloride. A similar reaction was carried out with the ethyl ester (**1446b**) in boiling ethanol in the presence of Amberlyst-15(H^+) resin (84MI7; 87MI4).



The Fischer glycosidation of *N*-(1-deoxy-D-fructos-1-yl)aminomethylenemalonate (**1448**) was carried out in a 1.25% solution of hydrogen chloride in methanol at ambient temperature to produce a mixture of fructofuranosides (**1449** and **1450**) and fructopyranoside (**1451**). The reaction was complete after 5 hr, but the glycoside equilibrium was attained only after 24 hr (86MI10).



2. REDUCTION, HYDROGENATION

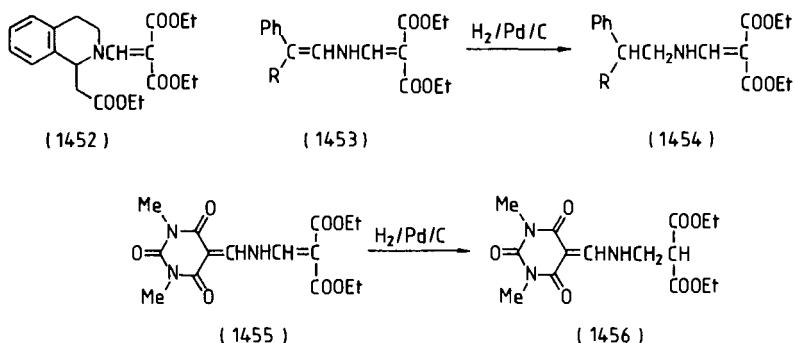
The hydrogenation of aminomethylenemalonates (**9**, $\text{R} = \text{R}^1 = \text{H}$, $\text{R} = \text{Ph}$, $\text{R}^1 = \text{H}$, Me , and **1452**) over platinum oxide or Raney nickel in ethanol resulted in reductive cleavage of the C—N bond to give the corresponding amine (46JA2009; 52JCS650; 64JMC68). In the case of the phenylamino derivative (**9**, $\text{R} = \text{Ph}$, $\text{R}^2 = \text{H}$), diphenylurea was also obtained in 4% yield (46JA2009). The *N*-methyl-*N*-phenylamino derivative (**9**, $\text{R} = \text{Ph}$, $\text{R}^1 = \text{Me}$) and the piperidino derivative (**274**, $n = 1$, $\text{X} = \text{CH}_2$) gave diethyl methylmalonate (46JA2009; 64JMC68).

The catalytic hydrogenation of 1-piperidinylmethylenemalonate (**274**, $n = 1$, $\text{X} = \text{CH}_2$) over platinum black in glacial acetic acid likewise gave diethyl methylmalonate (64JMC68).

The catalytic hydrogenation of *N*-(2-substituted 2-phenyl-vinyl)-aminomethylenemalonates (**1453**) over 10% palladium-on-charcoal at 70°C in dioxane gave *N*-(2-substituted 2-phenylethyl)aminomethylenemalonates (**1454**), while that of **1455** at 50°C afforded aminomethylmalonate (**1456**) (70AP612). The hydrogenation of **1456** under the previous conditions at 90°C yielded 1,3,5-trimethylbarbituric acid.

The catalytic reduction of *N*-(4-nitrophenyl)aminomethylenemalonate in methanol over a palladium catalyst gave *N*-(4-aminophenyl)aminomethylenemalonate in 67% yield [86JCR(S)161].

The nitro group of (1-isoquinolinylamino)methylenemalonate (**1457**, $\text{R} = \text{NO}_2$) was catalytically reduced over a 10% Pd/C catalyst in DMF to give the 4-amino derivative (**1457**, $\text{R} = \text{NH}_2$) [84JAP(K)172472].



The reduction of aminomethylenemalonates (**1458**) with lithium aluminum hydride (LAH) in diethyl ether or THF gave 2-aminomethyl-2-propen-1-ols (**1459**) in good yields (62JOC4137; 64JMC68; 66CB281).

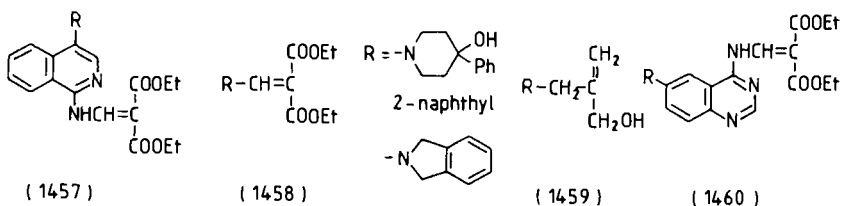
Earlier, Shivalkar and Sunthakar incorrectly reported that the reduction of diethyl 2-naphthylaminomethylenemalonate with LAH in diethyl ether gave 3-(2-naphthylamino)allyl alcohol in 46–90% yields (58MI3; 60JA718). Similar reactions were described for phenylaminomethylenemalonate, *N*-(2-aminophenyl)aminomethylenemalonate, and benzylaminomethylenemalonate (58MI3; 60JA718; 61MI2).

The reduction of diethyl *N*-ethyl-*N*-phenylaminomethylenemalonate, 2-pyridyl-, and 2-pyrimidinylaminomethylenemalonates with LAH in diethyl ether resulted in cleavage of the $=CH-N$ bond to afford the corresponding amines (60JA718).

N-(6-Nitro-4-quinazolinyl)aminomethylenemalonate (**1460**, $R = NO_2$) was hydrogenated in DMF in a hydrogen atmosphere over 10% palladium-on-carbon at ambient temperature for 1 hr to give the 6-amino derivative (**1460**, $R = NH_2$) (81EUP30156).

No reaction occurred when diethyl *N*-(1-ethoxycarbonyl-ethyl)aminomethylenemalonate was heated in ethanol in the presence of a zinc-copper couple (14JCS27).

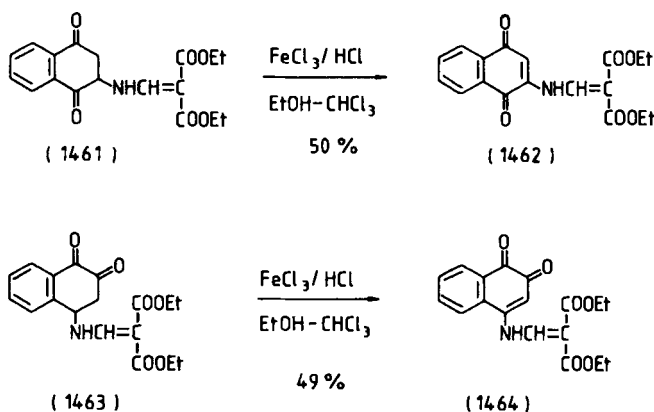
The reduction of diethyl *N*-(4-methylpiperazin-1-yl)methylenemalonate over a platinum catalyst with hydrogen or with sodium borohydride af-



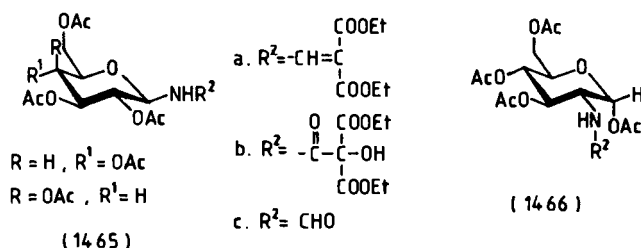
forded a mixture of 1-methylpiperazine and diethyl methylmalonate. The presence of diethyl methylenemalonate could also be detected when the catalytic reduction was carried out in ethanol (75ZOR420).

3. OXIDATION

Dihydro-1,4- and -1,2-naphthoquinone derivatives (**1461** and **1463**) in a mixture of ethanol and chloroform were oxidized with iron(III) chloride in dilute hydrochloric acid to naphthoquinones (**1462** and **1464**) (67JOC3210).



The oxidation of sugar enamines [**1465** and **1466**, $\text{R}^2 = -\text{CH}=\text{C}(\text{COOEt})_2$] with potassium permanganate and potassium metaperiodate in a 1:1 mixture of acetone and water at ambient temperature gave α -hydroxy amides [**1465** and **1466**, $\text{R}^2 = \text{COCO}(\text{COOEt})_2$] and *N*-formyl amino sugars (**1465** and **1466**, $\text{R}^2 = \text{CHO}$) 42–52% and 15–28% yields, respectively [89JCS(P1)1923].

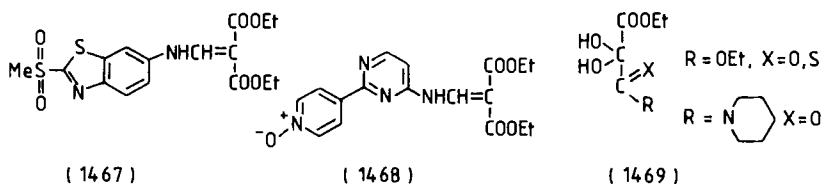


The methylthio group of 6-benzothiazolylaminomethylenemalonate (**271**) was oxidized to the methylsulfonyl group with potassium permanganate in aqueous acetic acid at ambient temperature for 2 hr to give the 2-methylsulfonyl derivative (**1467**) in 41% yield (76CPB130).

The treatment of diethyl *N*-[2-(4-pyridinyl)pyrimidin-4-yl]aminomethylenemalonate with *m*-chloroperbenzoic acid (85%) in methylene chloride at 0°C for 1 hr, and then at ambient temperature for 16 hr, gave the *N*-oxide (**1468**) in 64% yield (77USP4018770, 77USP4032523).

N,N-Dimethylaminomethylenemalonates (**331**) were photooxidized in deuteriochloroform at 25°C for 20 hr to give 2-oxomalonates (**1469**) as the dihydrates in 65–84% yields (84TL3743).

Diethyl *N*-(6-methyl-3-pyridinyl)aminomethylenemalonate was oxidized to the *N*-oxide (**987**, R = Me) with 40% peracetic acid in acetic acid at 55–60°C for 2 hr (69USP3429887).

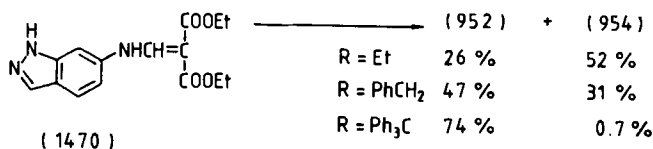


4. ALKYLATION

Dimethyl (methylthio)(phenylamino)methylenemalonate (**341**) was *N*-alkylated on the action of dimethyl sulfate in boiling acetone in the presence of potassium carbonate for 20 hr to give dimethyl (methylthio)(*N*-methyl-*N*-phenylamino)methylenemalonate in 98% yield (69T4649).

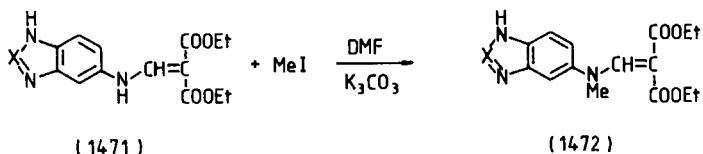
The ethylation of 6-indazolylaminomethylenemalonate (**1470**) with ethyl iodide in DMF at 80–85°C for 2 hr in the presence of potassium carbonate gave a 1 : 2 mixture of *N*-(1- and 2-ethyl-6-indazolyl)aminomethylenemalonates (**952** and **954**, R = Et) in 78% yield [77JHC1175; 78JAP(K)119895].

The reactions of 6-indazolylaminomethylenemalonate (**1470**) with benzyl chloride and with trityl chloride in a mixture of DMF and ethanol and



in ethanol, respectively, in the presence of sodium ethylate gave a mixture of 1- and 2-alkylated derivatives (**952** and **954**, $R = \text{PhCH}_2$ and Ph_3C) [78YZ1158; 79JAP(K)84596].

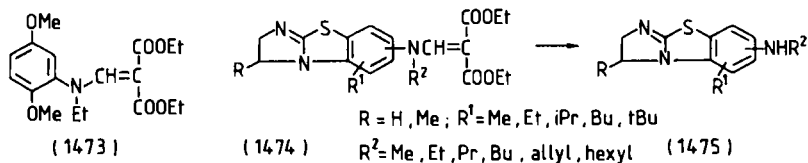
The amino group of 5-benzimidazolyl- and 5-benzotriazolylaminomethylenemalonates (**1471**, $X = \text{CH}$ and N) was alkylated with methyl iodide in DMF in the presence of potassium carbonate in 43–91% yields (89CCCC713). 5-Benzimidazolylaminomethylenemalonate (**1471**, $X = \text{CH}$) was also alkylated on the amino group with ethyl iodide and benzyl chloride, or with methyl iodide in dimethoxyethane, or dimethyl sulfate in THF in the presence of sodium hydride.



Diethyl *N*-(2,5-dimethoxyphenyl)aminomethylenemalonate was alkylated with ethyl iodide in DMF in the presence of sodium hydride to give the *N*-ethyl derivative (**1473**) in 42% yield (82HCA2645).

Diethyl *N*-(2-oxo-1-*H*-pyridin-3-yl)aminomethylenemalonate was alkylated with methyl iodide in DMF in the presence of potassium carbonate for 16 hr to give (1-methyl-2-oxo-1-*H*-pyridin-3-yl)aminomethylenemalonate (**985**) in 76% yield (81JHC941).

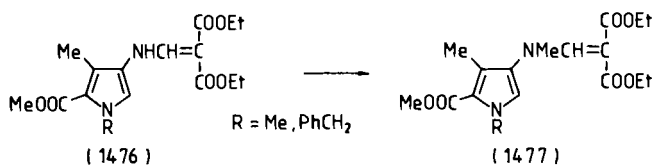
N-(2,3-Dihydroimidazo[2,1-*b*]benzothiazol-6-, 7- and 8-yl)aminomethylenemalonates (**1474**, $R^2 = \text{H}$) were alkylated with dialkyl sulfate or alkyl halide in hexamethylphosphortriamide in the presence of sodium hydride to give *N*-alkyl-*N*-(2,3-dihydroimidazo[2,1-*b*]benzothiazolyl)aminomethylenemalonates (**1474**, $R^2 \neq \text{H}$). The hydrolysis of **1474** by heating in boiling dilute hydrochloric acid for 15 min gave alkylamino derivatives (**1475**) (81EUP21806).



2-Thienylaminomethylenemalonates were ethylated with ethyl *p*-toluenesulfonate in the presence of potassium carbonate (85EUP161235) and potassium hydroxide (87MI3) in DMF to afford *N*-ethyl derivatives (**711**, $R = \text{H}, \text{Me}$) in 80% and 41–48% yields, respectively.

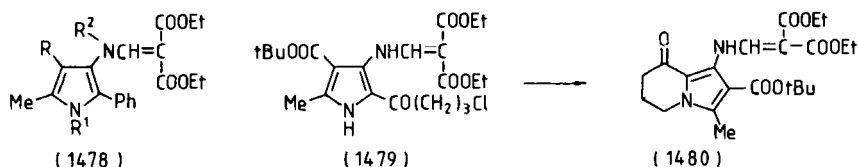
Diethyl *N*-(2,3,4-trifluorophenyl)aminomethylenemalonate was alkylated in the presence of sodium hydride in DMF to give diethyl *N*-substituted *N*-(2,3,4-trifluorophenyl)aminomethylenemalonates [85JAP(K) 166681].

N-(1-Methyl- and 1-benzyl-3-pyrrolyl)aminomethylenemalonates (**1476**, $R = \text{Me}, \text{CH}_2\text{Ph}$) were obtained in 91% and 91% yields, respectively, when 3-pyrrolylaminomethylenemalonate (**1476**, $R = \text{H}$) was reacted with methyl iodide or with benzyl bromide in DMF in the presence of sodium methylate at ambient temperature for 10–60 min (85JHC83; 89JHC1029). *N*-Methyl derivatives (**1477**) were prepared in nearly quantitative yield under the previous conditions with methyl iodide if the reaction mixtures were stirred overnight.



The reactions of 3-pyrazolylaminomethylenemalonate (**1478**, $R = R^1 = R^2 = \text{H}$) with dimethyl sulfate, ethyl iodide, or benzyl bromide in boiling THF in the presence of sodium hydride yielded *N*-substituted *N*-(3-pyrazolyl)aminomethylenemalonates (**1478**, $R = R^1 = \text{H}, R^2 = \text{Me}, \text{Et}, \text{PhCH}_2$). 3-Pyrazolylaminomethylenemalonate (**1478**, $R = \text{COO}^i\text{Bu}, R^1 = R^2 = \text{H}$) was dimethylated with methyl iodide in DMF in the presence of sodium methylate at room temperature overnight to give *N*-methyl-*N*-(1,5-dimethyl-3-pyrazolyl)aminomethylenemalonate (**1478**, $R = \text{COO}^i\text{Bu}, R^1 = R^2 = \text{Me}$) in 88% yield (85JHC729).

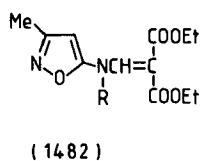
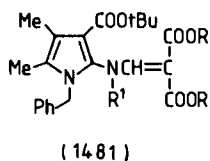
The treatment of *N*-[2-(4-chlorobutyryl)-3-pyrrolyl]aminomethylenemalonate (**1479**) with potassium *tert*-butoxide in THF at ambient temperature for 2 hr afforded 1-indolizinyllaminomethylenemalonate (**1480**) in 94% yield (85JHC817).



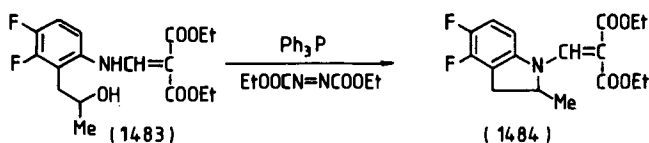
The *N*-methyl derivatives (**1481**, $R^1 = \text{Me}$) were prepared from 2-pyrrolylaminomethylenemalonates (**1481**, $R^1 = \text{H}$) with methyl iodide in DMF at ambient temperature for 2–4 days (85JHC1429).

The sodium salt of mercapto[phenylamino]methylenemalonate (**342**, R = 4-acetyl-1-piperidinyl, X = Na) in THF was added dropwise to a solution of methylene iodide in DMF in the presence of potassium carbonate at 60°C for 2 hr to give diethyl (1,3-thiazetidin-2-ylidene)malonate (**1291**) in 50% yield (87BRP2190376).

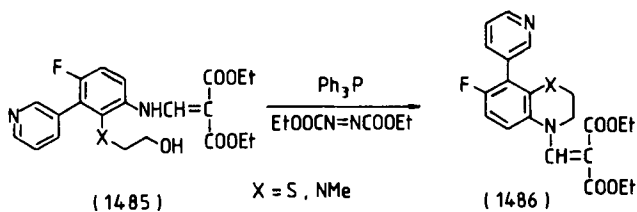
5-Isoxazolylaminomethylenemalonate (**1482**, R = H) was ethylated with ethyl iodide in DMF in the presence of potassium carbonate at ambient temperature overnight to afford the *N*-ethyl derivative (**1482**, R = Et) in 84% yield (88JHC231).



1-Indolylmethylenemalonate (**1484**) was obtained in 92% yield from *N*-[3, 4 - difluoro - 2 - (2 - hydroxypropyl phenyl) aminomethylenemalonate (**1483**) by the action of a mixture of triphenylphosphine and diethyl azodicarboxylate in THF at -20°C (88JHC1567).

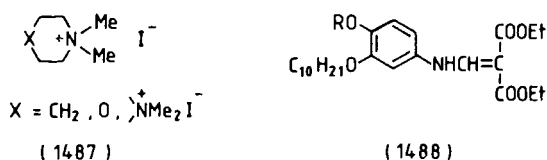


A solution of phenylaminomethylenemalonate (**1485**) in THF was added to a solution of triphenylphosphine and diethyl azodicarboxylate in THF at -20°C. The reaction mixture was warmed to room temperature, diluted with water, and extracted with ethyl acetate to give methylenemalonate (**1486**) in 75–99% yields (87USP4636506).

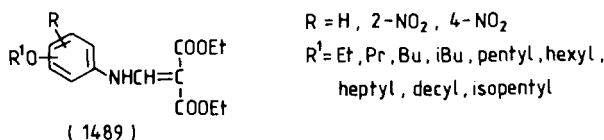


When diethyl (cyclic amino)methylenemalonates (**274**, $n = 1$, $X = \text{CH}_2$, O, NMe) were reacted with methyl iodide in boiling isobutyl alcohol, quaternary ammonium iodides (**1487**) were obtained (64JMC68).

N-(3-Decyloxy-4-hydroxyphenyl)aminomethylenemalonate (**1488**, $R = \text{H}$) was treated with sodium hydroxide in toluene and was then reacted with cyclopropylmethyl chloride in the presence of a catalytic amount of sodium iodide in DMF at 120–125°C for 2 hr to give the 3-decyloxy-4-cyclopropylmethoxyphenyl derivative (**1488**, $R = \text{cPrCH}_2\text{O}$) (74GEP-2431584, 74NEP8800).

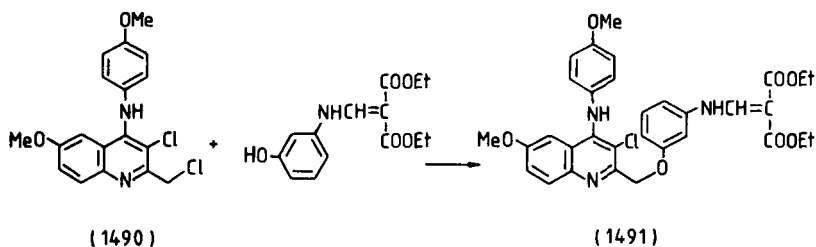


N-(Hydroxyphenyl)aminomethylenemalonates (**1489**, $R^1 = \text{H}$) were *O*-alkylated with alkyl bromides in DMF in the presence of potassium carbonate at 100°C for 3 hr (87YZ123).



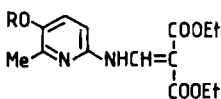
The reaction of diethyl *N*-(2-hydroxy-3,4-difluorophenyl)aminomethylenemalonate and benzyl bromide in DMF in the presence of sodium carbonate at ambient temperature for 2 hr afforded diethyl *N*-(2-benzyl-oxy-3,4-difluorophenyl)aminomethylenemalonate (88EUP259804).

N-(3-Hydroxyphenyl)aminomethylenemalonate was reacted with 2-chloromethylquinoline (**1490**) in 75% aqueous ethanol in the presence of potassium carbonate for 8 hr to give **1491** in 40% yield [82IJC(B)444].

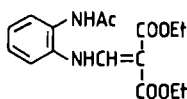


N-(5-Hydroxy-6-methyl-2-pyridyl)aminomethylenemalonate (**1492**, R = H) was alkylated with alkyl halides in DMF in the presence of potassium carbonate at 90–110°C for 1 hr to give the 5-alkoxy derivatives (**1492**, R = Et, *i*Pr, CH₂Ph, CH₂OMe) [81JAP(K)131583].

Diethyl *N*-(2-hydroxyphenyl)aminomethylenemalonate was reacted with 2,4-dinitro-1-chlorobenzene in boiling aqueous ethanol in the presence of sodium hydrogen carbonate for 4 hr. After work-up, 2-hydroxy-2',4'-dinitrodiphenylamine, obtained in 76% yield, failed to react with EMME under the usual conditions (89CCC506).



(1492)



(1493)

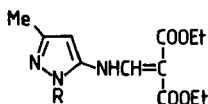
5. ACYLATION, DEACYLATION

Diethyl aminomethylenemalonate (**13**) was *N*-acylated with acetic anhydride (75JHC1245).

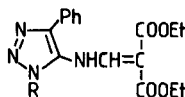
Diethyl *N*-(2-Aminophenyl)aminomethylenemalonate was acetylated by treatment with acetic anhydride at room temperature to give the 2-acetamido derivative (**1493**) in 78% yield (59MI1).

The treatment of 5-pyrazolylaminomethylenemalonate (**1494**, R = H) with acetyl chloride in pyridine gave the 1-acetyl derivative (**1494**, R = Ac) in 66% yield (74AP177).

The reaction of *N*-(1,2,3-triazol-5-yl)aminomethylenemalonate (**1495**, R = H) and acetic anhydride afforded the 1-acetyl derivative (**1495**, R = Ac) in 95% yield [71JCS(C)2156].



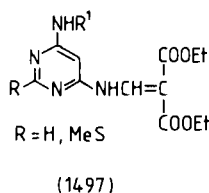
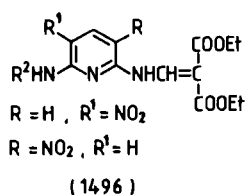
(1494)



(1495)

N-(4-Amino-1-isoquinoliny)aminomethylenemalonate (**1457**, R = NH₂) was acetylated with acetic anhydride in pyridine at ambient temperature to give the 4-acetamido derivative (**1457**, R = NHAc) [84JAP(K)172472].

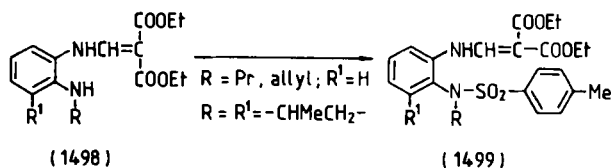
N-(6-Amino-2-pyridyl)aminomethylenemalonates (**1496**, R² = H) were



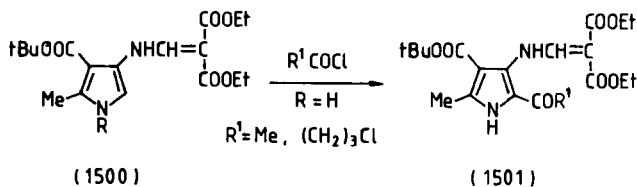
acylated by treatment with acetyl chloride in pyridine at 80°C for 1 hr afford the 6-acetamido derivatives (**1496**, $R^2 = \text{Ac}$) in 50–70% yields (72G253).

The reaction of *N*-(6-amino-4-pyrimidinyl)aminomethylenemalonates (**1497**, $R^1 = \text{H}$) and acetic anhydride at reflux temperature overnight gave the 6-acetamido derivatives (**1497**, $R^1 = \text{Ac}$) in 60–68% yields (72JOC3980).

The treatment of *N*-(2-aminophenyl)aminomethylenemalonates (**1498**) with tosyl chloride in pyridine afforded *p*-toluenesulfonyl derivatives (**1499**) in 64–73% yields [75JCS(P1)2409].



The reaction of 3-pyrrolylaminomethylenemalonate (**1500**, $R = \text{H}$) and acetic anhydride at reflux temperature for 1 hr gave (1-acetyl-3-pyrrolyl)aminomethylenemalonate (**1500**, $R = \text{Ac}$) in 81% yield. When **1500** ($R = \text{H}$) was acylated with acyl chlorides in a mixture of pyridine and THF at reflux temperature for 2–4 hr, the 5-acyl derivatives (**1501**) were obtained in 51–67% yields (85JHC817).

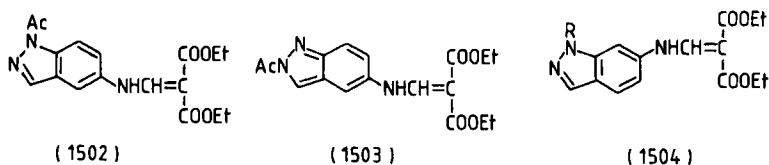


The treatment of 5-indazolylaminomethylenemalonate (**948**, $R = \text{H}$) with acetic anhydride in acetic acid in the presence of pyridine for 1.5 hr gave the 1-acetyl derivative (**1502**) in 97% yield, while in THF in the

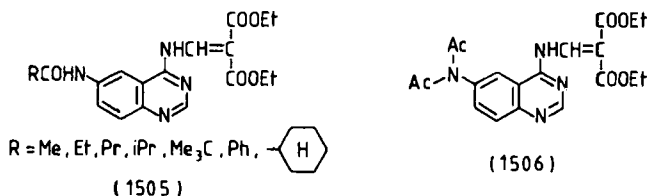
presence of pyridine for 1 hr, it afforded a 1 : 8 mixture of the isomeric 1- and 2-acetyl derivatives (**1502** and **1503**) in 96% yield [78YZ1063; 79JAP(K)32496].

N-(2-Acetyl-5-indazolyl)aminomethylenemalonate (**1503**) was isomerized to the 1-acetyl derivative (**1502**) in 90% yield by heating in toluene for 4 hr [78YZ1063; 79JAP(K)32496].

The acylation of 6-indazolylaminomethylenemalonate (**1470**) by reaction with acetic anhydride in the presence of pyridine for 45 min, or with benzoyl chloride in a mixture of DMF and benzene in the presence of sodium ethylate for 75 min, gave 1-acyl derivatives (**1504**) in 72% and 58% yields, respectively (78YZ1158).

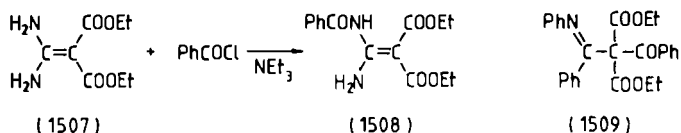


The reaction of *N*-(6-amino-4-quinazoliny)aminomethylenemalonate (**1460**, R = NH₂) and acyl chloride in methylene chloride in the presence of pyridine at 0°C afforded the 6-acylamido derivatives (**1505**) (81EUP30156). When the amine (**1460**, R = NH₂) was repeatedly reacted with acetic anhydride in pyridine, the *N,N*-diacetylamino derivative (**1506**) was obtained. Treatment of the amine (**1460**, R = NH₂) with pivaloyl chloride in methylene chloride in the presence of pyridine gave the pivaloylamido derivative (**1505**, R = Me₃C—), while in DMF in the presence of pyridine a mixture of the pivaloylamido and 6-formamido derivatives (**1505**, R = Me₃C— and H) was obtained.

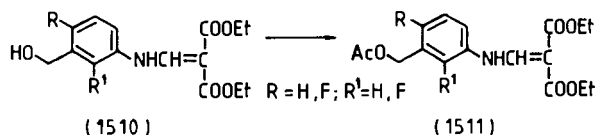


The reaction of bis(amino)methylenemalonate (**1507**) and benzoyl chloride in the presence of triethylamine in boiling chlorobenzene for 5 hr afforded amino(benzoylamido)methylenemalonate (**1508**) in 65% yield (77ZOR954).

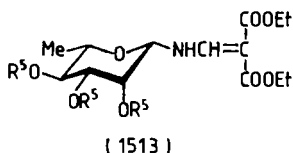
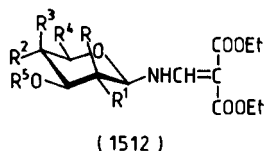
Benzoylation of (phenylamino)phenylmethylenemalonate (**4**) with benzoyl chloride in diethyl ether in the presence of sodium at reflux temperature gave the 2-benzoylmalonate derivative (**1509**) (36JCS428).



The reaction of *N*-(3-hydroxymethylphenyl)aminomethylenemalonates (**1510**) and acetic anhydride by heating in acetic acid at 55–60°C for 20 hr gave the 3-acetoxymethyl derivatives (**1511**) in 71–97% yields (82CPB3517, 82CPB3530).



The hydroxy groups of pyranosylaminomethylenemalonates (**1512–1514**, $\text{R}^5 = \text{H}$) were acetylated with a mixture of acetic anhydride and pyridine (68M11). *N*-(2,3,4,6-Tetra-*O*-acetylglucopyranosyl)aminomethylenemalonate (**1512**, $\text{R} = \text{R}^3 = \text{H}$, $\text{R}^1 = \text{R}^2 = \text{OR}^5$, $\text{R}^4 = \text{CH}_2\text{OR}^5$, $\text{R}^5 = \text{Ac}$) was deacetylated in ethanol with sodium ethylate.

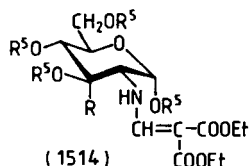


$\text{R} = \text{R}^3 = \text{H}; \text{R}^1 = \text{R}^2 = \text{OR}^5; \text{R}^4 = \text{CH}_2\text{OR}^5; \text{R}^5 = \text{H, Ac}$

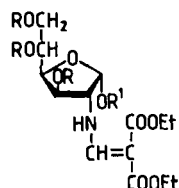
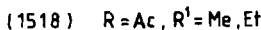
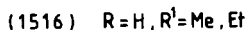
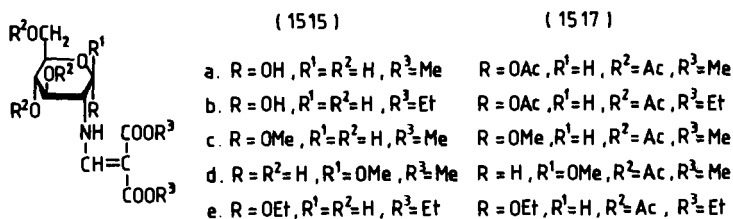
$\text{R} = \text{R}^2 = \text{OR}^5; \text{R}^1 = \text{R}^3 = \text{H}; \text{R}^4 = \text{CH}_2\text{OR}^5; \text{R}^5 = \text{H, Ac}$

$\text{R} = \text{R}^2 = \text{H}; \text{R}^1 = \text{R}^3 = \text{OR}^5; \text{R}^4 = \text{CH}_2\text{OR}^5; \text{R}^5 = \text{H, Ac}$

$\text{R} = \text{R}^3 = \text{R}^4 = \text{H}; \text{R}^1 = \text{R}^2 = \text{OR}^5; \text{R}^5 = \text{H, Ac}$

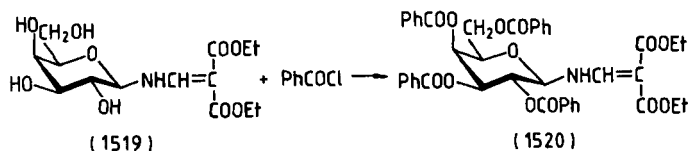


The aminomethylenemalonate derivatives of pyranoses (**1515**) and furanosides (**1516**) were acylated with acetic anhydride in pyridine at 0°C for 24 hr to give tri- and tetraacetylated products (**1517** and **1518**) in high yields (84M17; 87M14).

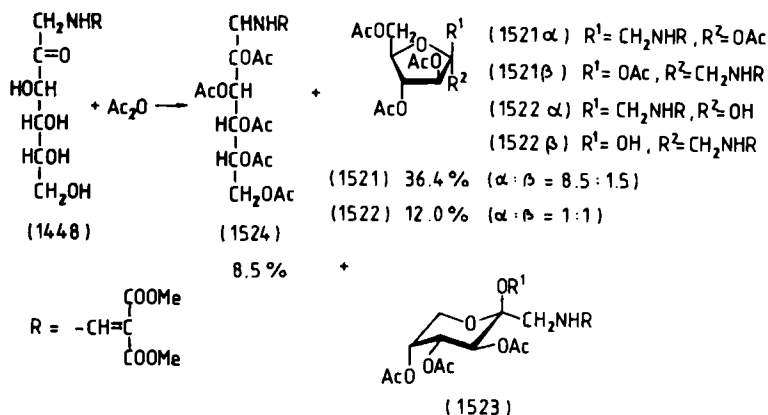


3,4,6-Tri-*O*-acetyl derivatives of glucopyranoses (**1517**, $R = OH$, $R^1 = H$, $R^2 = Ac$, $R^3 = Me, Et$) were obtained from **1515** ($R = OH$, $R^1 = R^2 = H$, $R^3 = Me, Et$) by the treatment with acetyl chloride in chloroform (88M14).

N-(β -D-Galactopyranosyl)aminomethylenemalonate (**1519**) was treated with benzyl chloride in pyridine at 0°C for 24 hr at ambient temperature, to give the tetra-*O*-benzoyl derivative (**1520**) in 96% yield (86M18).



The acetylation of *N*-(1-deoxy-D-fructos-1-yl)aminomethylenemalonate (**1448**) with acetic anhydride in pyridine at 0–20°C for 4 days gave a mixture of tetraacetates of fructofuranosides (**1521**), triacetates of fructofuranosides (**1522**), and fructopyranose (**1523**, $R^1 = H$) and the pentaacetyl-*arabino*-hex-1-enitol derivative (**1524**) (Scheme 57) (86M110). Further treatment of **1524** with acetic anhydride in pyridine gave a mixture of tetraacetates of fructofuranosides (**1521**) and the starting compound **1524**.

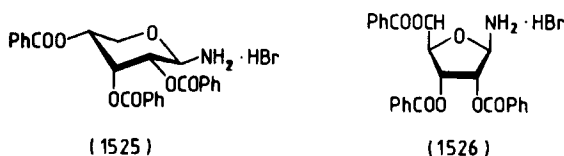


SCHEME 57

A mixture of triacetyl- α -D-fructofuranoside (1521, α , $\text{R}^2 = \text{OMe}$) and triacetyl- β -D-fructopyranoside (1523, $\text{R}^1 = \text{Me}$) was obtained when the crude glycoside mixture obtained in the glucosidation of 1448 in methanol containing 1% hydrogen chloride at room temperature for 5 hr was acetylated with acetic anhydride in the presence of pyridine at 0°C for 3 days (86MI10). The Zemplen deacetylation of 1521 ($\text{R}^2 = \text{OMe}$) was carried out in quantitative yield.

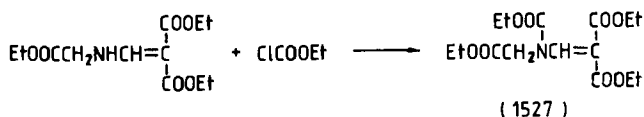
N-(β -D-Ribofuranosyl)aminomethylenemalonate (42) was acetylated by treatment with acetic anhydride in pyridine to give the 2,3,5-tri-*O*-acetyl derivative in 91% yield (88MI1).

The treatment of *N*-(β -D-ribofuranosyl)- and *N*-(β -D-ribofuranosyl)aminomethylenemalonates (41 and 42) with benzoyl chloride in pyridine, and then with a 4% solution of bromine in wet chloroform for 24 hr at room temperature, gave tri-*O*-benzoyl- β -D-ribofuranosylamine and tri-*O*-benzoyl- β -D-ribofuranosylamine hydrobromides (1525 and 1526) in 86 and 84% yields, respectively (88MI1).

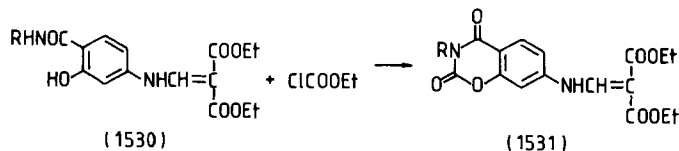
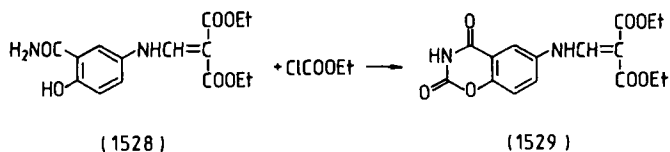


The acylation of diethyl *N*-ethyl-*N*-(2-thienyl)aminomethylenemalonate with acetic anhydride and propionic anhydride in the presence of AlCl_3 in methylene chloride gave the 5-acyl-2-thienyl derivatives in 35% and 40% yields, respectively (88MI12).

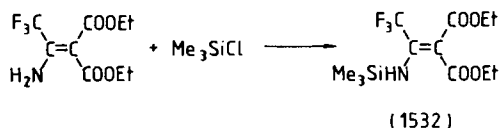
Diethyl *N*-(ethoxycarbonylmethyl)aminomethylenemalonate was reacted first with sodium hydride and then with ethyl chloroformate in dry benzene at reflux temperature for 2 hr to give the tetraester (**1527**) in 76% yield (78CPB2224).



N-(1,3-Benzoxazinyl)aminomethylenemalonates (**1529** and **1531**) were obtained in 70–87% yields when *N*-(3- and 4-carbamoyl-4- and 3-hydroxyphenyl)aminomethylenemalonates (**1528** and **1530**) were first treated with ethyl chloroformate dropwise in a mixture of pyridine and acetonitrile at 0–5°C. After refluxing the mixtures for 2 hr, the low-boiling solvent was removed under reduced pressure and the residues again were refluxed at about 125°C for 1 hr (75IJC1275).



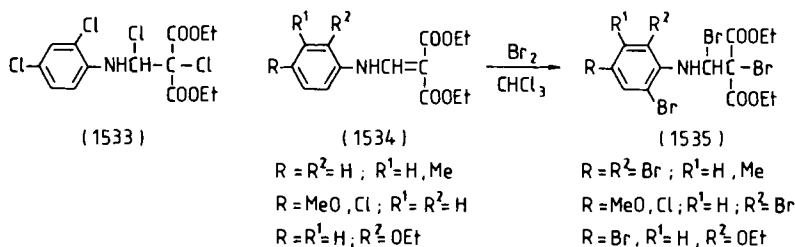
Diethyl amino(trifluoromethyl)methylenemalonate was reacted with trimethylsilyl chloride in boiling benzene in the presence of triethylamine for 3 hr to give the *N*-trimethylsilyl derivative (**1532**) in 90% yield (81ZOR439).



6. HALOGENATION

The tetrachloro derivative (**1533**) was obtained from the reaction of sulfonyl chloride on diethyl phenylaminomethylenemalonate and its *o*- and *p*-chloro derivatives in chloroform in the presence of a catalytic amount of iodide at ambient temperature (55MI1).

The bromination of arylaminomethylenemalonates (**1534**) with bromine in chloroform at ambient temperature resulted in saturation of the carbon-carbon double bond in the side chain and substitution of the aromatic ring in the *ortho* and *para* positions. The tetrabrominated products (**1535**) were highly unstable and were sensitive to moisture (55JIC52). In the case of the *m*-nitro derivative (**1534**, $\text{R} = \text{R}^2 = \text{H}$, $\text{R}^1 = \text{NO}_2$), only bromine addition took place (55JIC52; 57JIC817).



If the bromination of phenylaminomethylenemalonates was carried out in acetic acid with bromine, only substitution of the aromatic ring occurred and, depending on the molar ratio and the reaction period, *p*-bromo or *o,p*-dibromo derivatives were obtained (57JIC817). From *N*-(*m*-nitrophenyl)aminomethylenemalonate, only 3-nitro-6-bromoaniline was obtained.

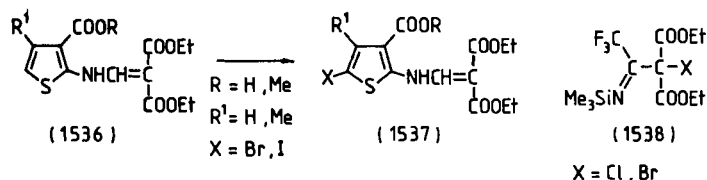
Diethyl aminomethylenemalonate (**13**) decomposed to diethyl bromomalonate, ammonium bromide, and formic acid by the action of bromine in glacial acetic acid (14JCS27). A similar decomposition occurred on treatment with dry hydrogen chloride in benzene.

2-Thienylaminomethylenemalonates (**1536**) were brominated with bromine in a mixture of pyridine and chloroform to yield the 5-bromo deriva-

tives (**1537**, X = Br) [75GEP2435025, 75JAP(K)77393, 75JAP(K)77394; 87MI3].

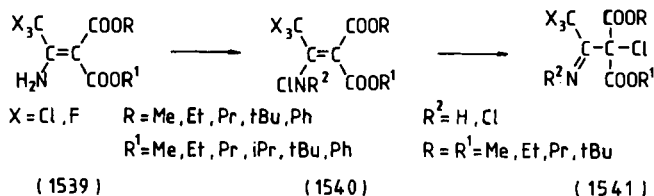
N-(5-Iodo-2-thienyl)aminomethylenemalonate (**1537**, R = Me, R¹ = H, X = I) was prepared from aminomethylenemalonate (**1536**, R = Me, R¹ = H) by treatment with iodine in chloroform in the presence of mercury(II) oxide at ambient temperature for 3 hr [75GEP2435025, 75JAP(K)77393, 75JAP(K)77394; 87MI3].

The reaction of (trimethylsilylamino)(trifluoromethyl) methylenemalonate (**1532**) and *tert*-butyl hypochlorite or *N,N*-dibromobenzene-sulfonamide in benzene afforded 2-halogen derivatives of the malonate (**1538**) in 92% and 85% yields, respectively (81ZOR439).

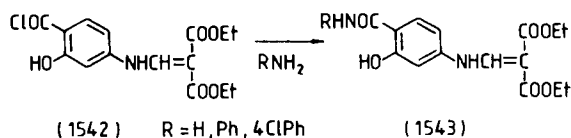


Amino(trihalomethyl)methylenemalonates (**1539**) were chlorinated with chlorine in carbon tetrachloride, with *tert*-butyl hypochlorite in benzene, and phosphorus pentachloride or *N,N*-dichlorobenzenesulfonamide in dichloroethane (68ZOR1710; 75ZOB873). Depending on the molar ratio, *N*-mono- or *N,N*-dichloro derivatives (**1540**, R² = H, Cl) were obtained.

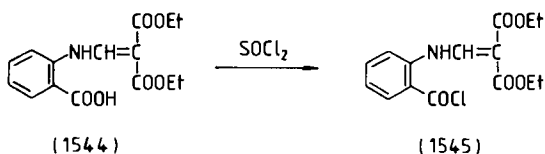
The reaction of aminomethylenemalonates (**1540**, R² = H, Cl) and *tert*-butyl hypochlorite gave the 2-chloro derivatives of the malonates (**1541**) (79ZOR1552).



The treatment of diethyl *N*-(4-carboxy-3-hydroxyphenyl)aminomethylenemalonate with thionyl chloride at reflux for 2 hr afforded the acid chloride (**1542**), which then was reacted with ammonium hydroxide or anilines in dry acetone at ambient temperature for 1 hr to give the corresponding amide (**1543**) (75IJC1275).



N-(2-Carboxyphenyl)aminomethylenemalonate (**1544**) was reacted with thionyl chloride to yield the corresponding acid chloride (**1545**) (73IJC1332).

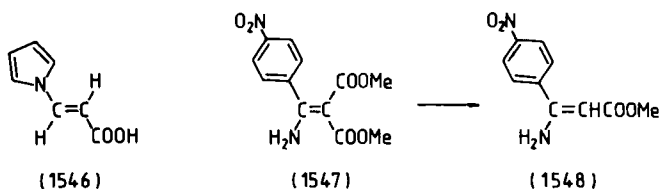


The treatment of aminomethylenemalonate derivative of α -D-glucopyranose (**40**, R = OH, R¹ = R² = H, R³ = Et) by acetyl bromide in chloroform at ambient temperature gave 1-bromo-3,4,6-triacetyl derivative (**40**, R = Br, R¹ = H, R² = Ac, R³ = Et). The latter was converted to methyl β -D-glucopyranoside (**40**, R = H, R¹ = OMe, R² = Ac, R³ = Et) by treatment with methanol in the presence of AgCO₃ (88MI4).

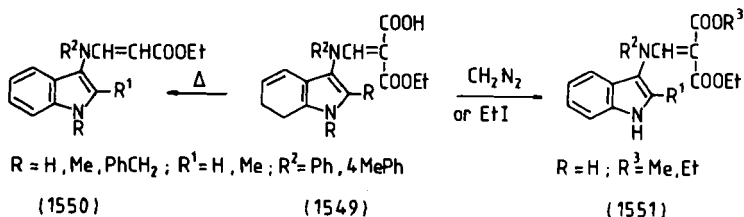
7. DECARBOXYLATION

The decarboxylation of 1-pyrrolylmethylenemalonic acid (**118**) in boiling toluene in the presence of a few drops of pyridine for 20 min afforded 3-(1-pyrrolyl)acrylic acid (**1546**) in 32% yield (82CB714).

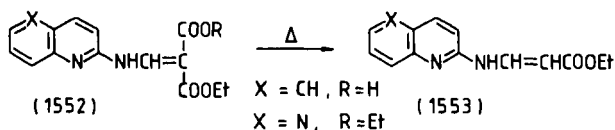
An aqueous methanolic solution of (3-nitrophenyl)aminomethylenemalonate (**1547**) was boiled in the presence of potassium hydroxide for 8 hr to give 3-amino-3-(3-nitrophenyl)acrylate (**1548**) in 53% yield (87EUP228845).



The half esters (**1549**) were decarboxylated to give 3-(3-indolylamino)-acrylates (**1550**) in 31–58% yields. The half esters (**1549**) were esterified by treatment with diazomethane in THF, or the sodium salts of **1549** were treated with ethyl iodide in hexamethylphosphortriamide to give the corresponding diester (**1551**) in 50–58% yields (82ZOR2001; 83ZOR1518).



The half ester of *N*-(2-quinoliny)aminomethylenemalonate (**1552**, X = CH, R = H) was decarboxylated by heating at 170–190°C for 30 min to afford 3-(2-quinolinylamino)acrylate (**1553**, X = CH) in 39% yield (74MIP1).



The heating of diethyl *N*-(1,5-naphthyridin-2-yl)aminomethylenemalonate (**1552**, X = N, R = Et) in boiling dimethyl sulfoxide for 3 hr gave 3-(1,5-naphthyridin-2-yl)acrylate (**1553**, X = N) in 64% yield (78MI7).

N-(3-Carboxyl-2-thienyl)aminomethylenemalonate (**56**, R = R¹ = H) was decarboxylated by heating in quinoline at 180–200°C for 1 hr to give 2-thienylaminomethylenemalonate (**57**, R = R¹ = H) in 66% yield (76GEP2447477).

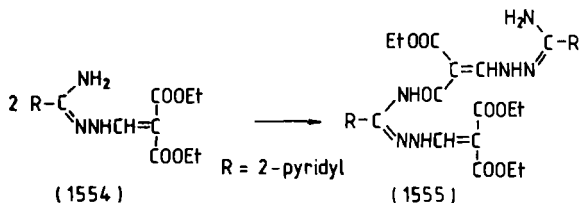
When *N*-(3-carboxyfuro[3,2-*b*]pyridin-2-yl)aminomethylenemalonate (**1432**, R = H) was heated in Dowtherm A at 190–200°C, only decarboxylation took place. No cyclization occurred. At higher temperature (about 240°C) **1432** (R = H) decomposed (84G211).

8. MISCELLANEOUS

From the diethyl *N*-(ethoxycarbonylmethyl)aminomethylenemalonate, diethyl (aminocarbonylmethylamino)methylenemalonate was obtained with aqueous ammonium hydroxide at ambient temperature, while ethyl

phenylaminomethylenemalonamate (**12**) was prepared by heating with aniline (14JCS27).

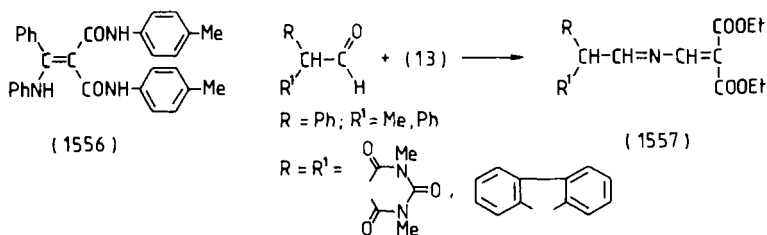
The heating of the amidrazone derivative (**1554**) in boiling toluene for 9 hr gave **1555** in 45% yield (77BCJ957).



(Phenylamino)phenylmethylenemalono-(di-*p*-toluidine) (**1556**) was prepared when diethyl (phenylamino)phenylmethylenemalonate (**4**) was heated at 110–120°C in the presence of *p*-toluidine (36JCS428).

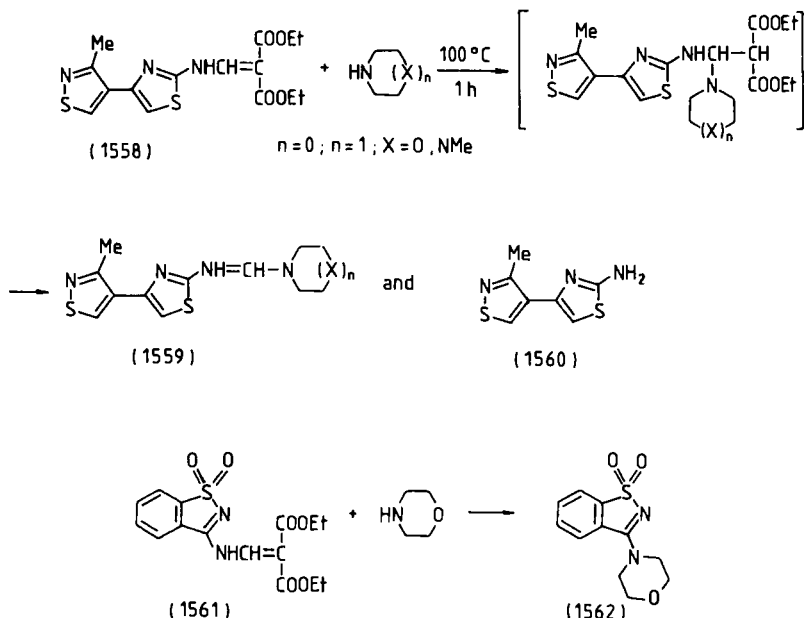
The reaction of diethyl phenylaminomethylenemalonate and aniline in *N*-methylpyrrolidine on heating at 180°C for 6 hr in the presence of trifluoroacetic acid under nitrogen gave ethyl phenylaminomethylenemalonamate (**12**) in 66% yield (78M12). Arylaminoethylenemalonamate derivatives were prepared in the reactions of arylaminomethylenemalonates and anilines (46JA1246, 46JA1253; 50JCS607).

The reaction of diethyl aminomethylenemalonate (**13**) with acetaldehyde derivatives in xylene in the presence of *p*-toluenesulfonic acid afforded 3-azapentadienes (**1557**) (70AP612).

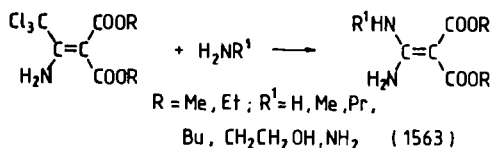


The reaction of aminomethylenemalonate (**1558**) with morpholine and with pyrrolidine gave a mixture of the amidine (**1559**) and the amine (**1560**), with an excess of the amidine (**1559**). In the case of *N*-methylpiperazine, only the amine (**1560**) was obtained (70IJC499).

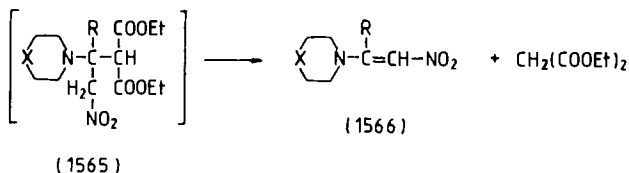
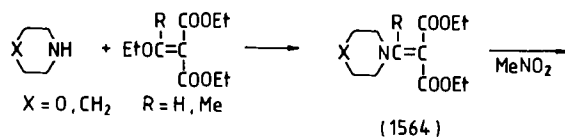
The reaction of 3-benzisothiazolylaminomethylenemalonate (**1561**) with morpholine at 100°C for 1 hr gave 3-(4-morpholinyl)-1,2-benzisothiazole-1,1-dioxide (**1562**) (70IJC499).



Dialkyl (1-amino-2,2,2-trichloroethylidene)malonates were reacted with amines or hydrazine hydrate in DMF to give (diaminomethylene) malonates (**1563**) (65JPR239; 77ZOR954).

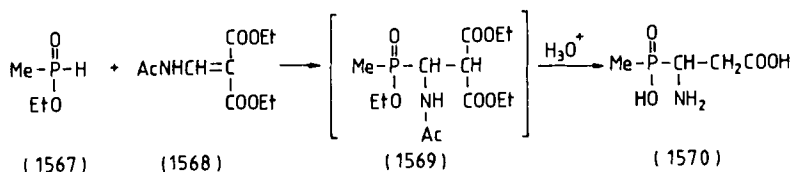


1-Nitro-2-amino-ethene and -propene derivatives (**1566**) were prepared in 21–40% yields in the reactions of EMME and diethyl 1-ethoxyethylidenemalonate and amine and nitromethane at reflux temperature for 2 hr (48JOC471). In the first step, aminomethylenemalonates (**1564**) were formed, which reacted with nitromethane in a base-catalyzed step to give addition products (**1565**). The latter decomposed immediately, as in the retrograde Michael reaction, to yield 1-nitro-2-aminoalkenes (**1566**). 1-Nitro-2-morpholinoethene (**1566**, $R = \text{H}$, $X = \text{O}$) was also prepared from morpholinomethylenemalonate (**1564**, $R = \text{H}$, $X = \text{O}$) and nitromethane in the presence of a catalytic amount of morpholine. Without a catalyst,

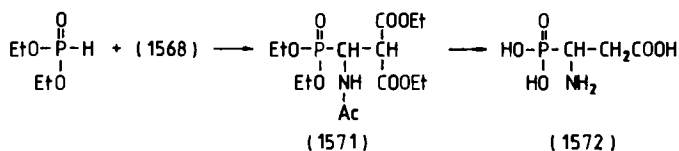


no reaction occurred. Dimethylamine, diethylamine, dipropylamine, pyrrolidine, and piperazine failed to give the corresponding 1-nitro-2-aminoalkenes.

The reaction of *O*-ethyl methylphosphinate (**1567**) and diethyl acetamidomethylenemalonate (**1568**) in the presence of sodium ethoxide gave an addition product (**1569**), which was then hydrolyzed with concentrated hydrochloric acid [74RC1119; 83PS(17)21].

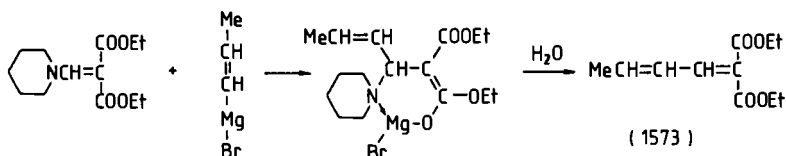


A 1 *M* or 2 *M* solution of sodium ethylate in ethanol was added dropwise at 60°C to a 1 : 1 mixture of acetamidomethylenemalonate (**1568**) and diethyl phosphite, while the temperature of the reaction mixture was raised to 100°C. At this temperature, the reaction mixture was stirred for 1.0–1.5 hr [76RC661; 88JCS(P1)61]. If the mixture was hydrolyzed with boiling concentrated hydrochloric acid overnight, 3-amino-3-phosphonopropionic acid (**1572**) was obtained in 75% yield (76RC661). When the cooled reaction mixture was treated with diethyl ether, then again boiled and filtered, and

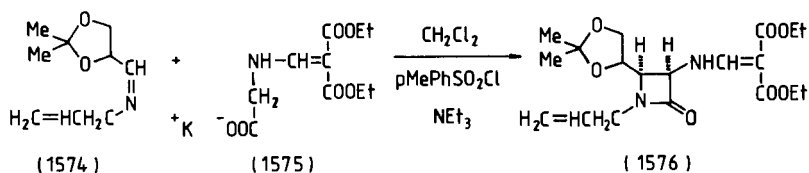


the filtrate was cooled to 0°C, the tetraester (**1571**) was obtained in 84% yield [88JCS(P1)61].

The malonic acid derivative (**1573**) was prepared from diethyl 1-piperidinylmethylenemalonate with propen-1-yl magnesium bromide at 0°C (61BSF2423).

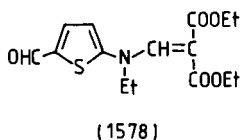
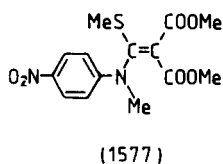


The reaction of isopropylidene-(*S*)-glyceraldehyde-*N*-allylimines (**1574**) and potassium *N*-(2,2-diethoxycarbonylvinyl)aminoacetate (**1575**) in methylene chloride in the presence of triethylamine or the action of *p*-toluenesulfonyl chloride at room temperature for 5 hr gave the corresponding 3-azetidinyaminomethylenemalonate (**1576**) in 29% yield (84EUP116854, 84EUP120289).

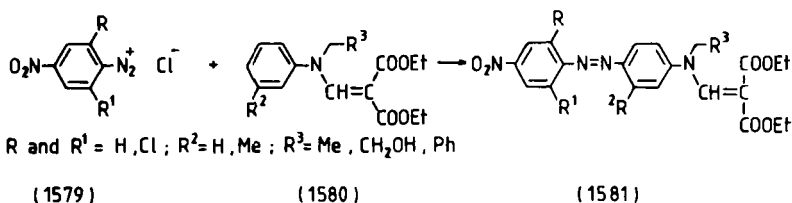


The nitration of dimethyl (*N*-phenyl-*N*-methylamino)methylthiomethylenemalonate with nitric acid in acetic acid at room temperature for 24 hr gave the 4-nitro derivative (**1577**) in 38% yield (69T4649).

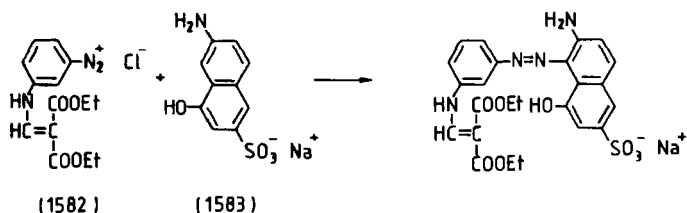
The formylation of diethyl *N*-ethyl-*N*-(2-thienyl)aminomethylenemalonate with phosphoryl chloride and *N*-methylformanilide or DMF in 1,2-dichloroethane for 2–5 hr gave the 5-formyl derivative (**1578**) in 70–89% yields (85EUP161235; 87MI3).



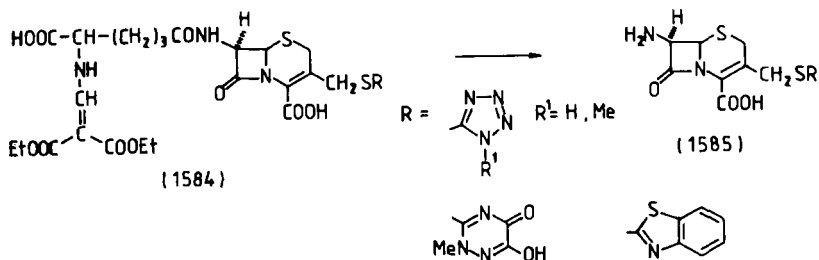
The reaction of *N*-aryl-*N*-alkylaminomethylenemalonates (**1580**) with diazonium chlorides (**1579**) in 30% hydrochloric acid at 0–10°C gave dyes (**1581**) (79MIP4).



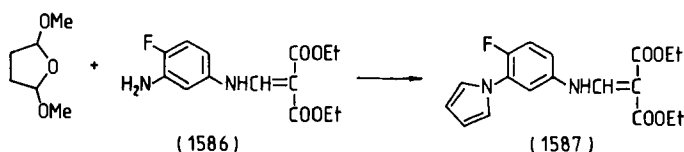
Diethyl *N*-(3-aminophenyl)aminomethylenemalonate (**165**, R = H) was diazotized, and the diazonium salt (**1582**) was then reacted with 2-aminonaphthalene (**1583**) at 0–10°C (80MI2).



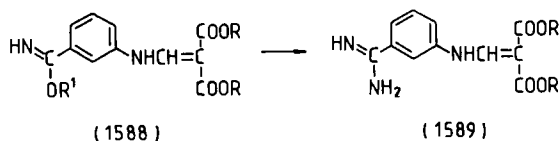
The *N*-(2,2-diethoxycarbonyl)vinyl derivative of cephalosporin C (**34**) was reacted with thiols in water at pH 6.5 at 60°C for 5–6 hr, or in boiling methylene chloride for 50 min, or in the absence of a solvent at 140°C for 15 min to give the mercapto derivatives (**1584**) (82EUP45717). When the mercapto derivatives (**1584**) first were reacted with dimethylaniline and dichlorodimethylsilane at 30°C for 10 min, the mixtures were then cooled to –10°C, and phosphorus pentachloride was added, followed by stirring at –5°C for 40 min, the 7-aminoceph-3-ene-4-carboxylic acid derivatives (**1585**) were obtained after work-up.



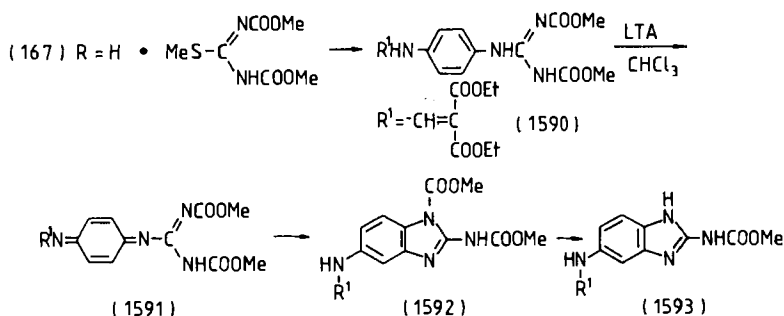
N-(4-Fluoro-3-aminophenyl)aminomethylenemalonate (**1586**) was reacted with dimethoxytetrahydrofuran in boiling glacial acetic acid for 3–4 min to give *N*-[4-fluoro-3-(1-pyrrolyl)phenyl]aminomethylenemalonate (**1587**) in 87% yield (86FRP2574404).



The treatment of dialkyl *N*-(3-cyanophenyl)aminomethylenemalonates with hydrogen chloride in a mixture of dioxane and an alcohol at 2–4°C for 7 days afforded imino ethers (**1588**) in 50–68% yields, which were then converted with ammonia in an alcohol into amidines (**1589**) in 70–78% yields (76PHA145).



Diethyl *N*-(4-Aminophenyl)aminomethylenemalonate (**167**, R = H) was reacted with *N,N'*-bis(methoxycarbonyl)-*S*-methylisothiourea in the presence of *p*-toluenesulfonic acid in boiling methanol for 4 hr to afford the guanidine derivative (**1590**) in 50% yield. The guanidine (**1590**) was oxidized in chloroform with lead tetraacetate to the quinoline diimine (**1591**), which cyclized to **1592**. After methanolysis, the 2-(methoxycarbonylamino)benzimidazole derivative (**1593**) was obtained in 41% yield [86JCR(S)161].



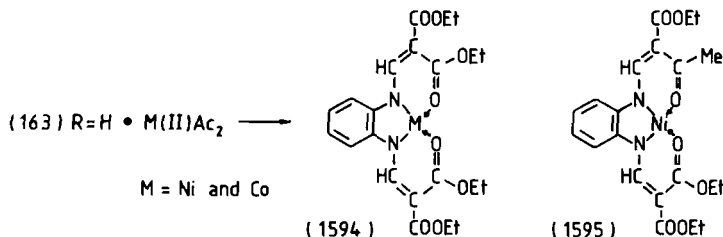
Diethyl *N*-(4-hydroxy-4-phenylpiperidin-1-yl)methylenemalonate did not react with ketene in acetone to give a cyclobutanone derivative (64JMC68).

The reaction of *N*-(4-ethoxyphenyl)thiourea and EMME at 150°C for 1.5 hr gave 4-ethoxyphenylisothiocyanate (68YZ1003).

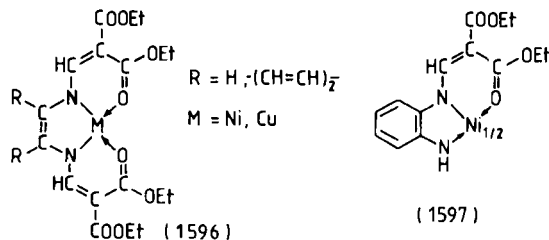
No reaction occurred between dimethyl acetylenedicarboxylate and morpholinomethylenemalonate in diglyme at room temperature (63JOC3134).

Bis(aminomethylenemalonate) (**163**, $R = H$) formed nickel and cobalt complexes (**1594**) with metal acetate in methanol in 75% and 90% yields, respectively (85ZC28).

The template condensation of diethyl *N*-(2-aminophenyl)aminomethylenemalonate (**162**, $R = H$), ethyl 2-[*N*-(2-aminophenyl)amino]methylenecoacetate, and Ni(II) acetate tetrahydrate in boiling ethanol for 20 hr gave a 60% yield of unsymmetrically substituted nickel(II) complexes of type **1595**, which were characterized by UV, 1H - and ^{13}C -NMR spectra (88M12).

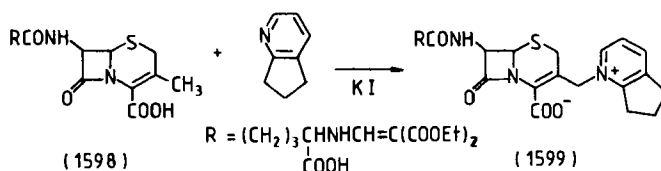


Bis-condensation products of 1,2-diaminoethylene and *o*-phenylenediamine with EMME gave stable 1 : 1 chelates (**1596**) with Cu(II) and Ni(II) acetate and Ni(II) acetylacetonate. Diethyl *N*-(2-aminophenyl)aminomethylenemalonate (**162**, $R = H$) and Ni(II) acetate formed a 2 : 1 chelate (**1597**) (67M11). The noncoordinated carboxy group could be hydrolyzed to the carboxy group with aqueous potassium hydroxide in methanol.

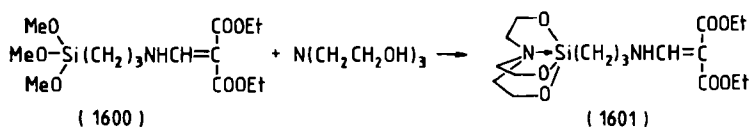


The reaction of cephalosporanic acid (**1598**) and cyclopenteno(*b*)pyridine in a 3 : 1 mixture of water and acetone in the presence of potassium iodide and ascorbic acid at 66–68°C for 4 hr gave the pyridiniumceph-3-ene-4-carboxylate derivative (**1599**) in 14% yield (84GEP3316796).

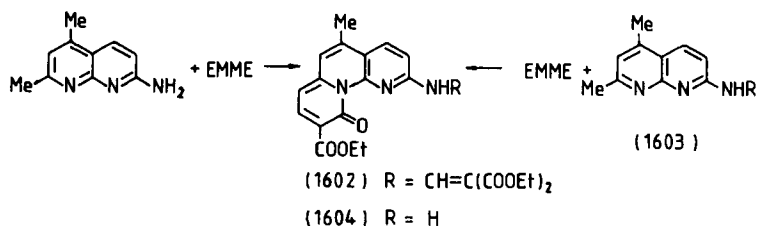
The reaction of *N*-[3-(trimethoxysilyl)propyl]aminomethylenemalonate



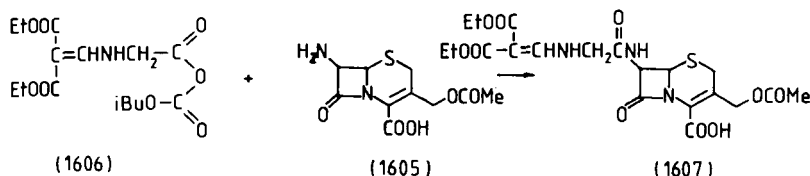
(1600) and tri(2-hydroxyethyl)amine afforded aminomethylenemalonate (1601), which inhibited the growth of adenocarcinoma 755 by 50–68% (82MI7).



The reaction of 2-amino-5,7-dimethyl-1,8-naphthyridine and EMME in boiling Dowtherm A for 45 min gave the pyrido[1,2-*a*]-1,8-naphthyridine derivative (1602) in 40% yield. The same product (1602) was obtained in 44% yield in the reaction of *N*-(1,8-naphthyridin-2-yl)aminomethylenemalonate (1603) and EMME in boiling Dowtherm A for 1 hr. The thermal ring closure of 1603 was unsuccessful. An ethanolic suspension of 1603 was treated with concentrated aqueous ammonium hydroxide at reflux for 24 hr to give 2-aminopyrido[1,2-*a*]-1,8-naphthyridine (1604) in quantitative yield (80FES1052).



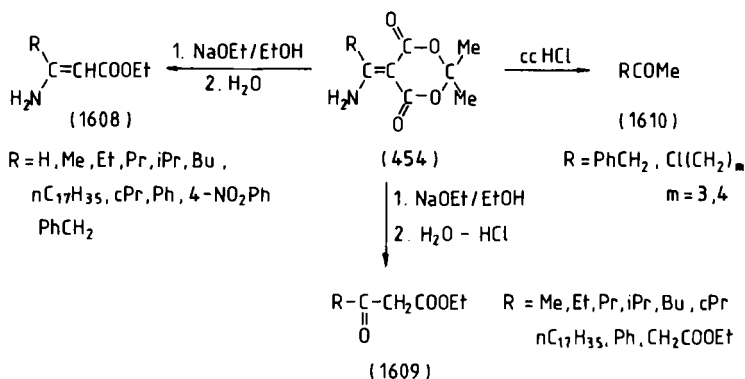
The triethylamine salt of 7-aminocephalosporanic acid (1605) was acylated at -5°C with anhydride 1606, prepared from diethyl (carboxymethylamino)methylenemalonate and isobutyl chloroformate in the presence of triethylamine at -15°C , to give compound 1607 in 62% yield (74GEP2362978).



B. Reactions of Alkylidene Aminomethylenemalonates

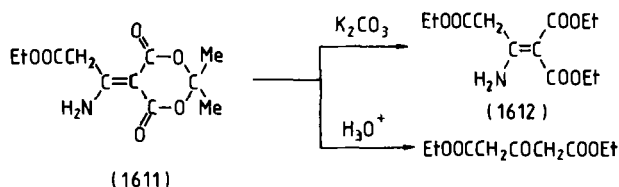
The treatment of isopropylidene phenylaminomethylenemalonate with 85% sulfuric acid at ambient temperature for 14 hr gave phenylaminomethylenemalonic acid in 42% yield (81CB3471).

Isopropylidene (1-aminoalkylidene)malonates (**454**) were heated under reflux in ethanol in the presence of sodium ethylate overnight. After evaporation of the solvent, the residues were treated with water to give 3-aminoacrylates (**1608**) in 48–89% yields. If the residues were treated with water and 10% hydrochloric acid, 3-oxo esters (**1609**) were obtained in 22–81% yields. When isopropylidene (1-aminoalkylidene)malonates (**454**) were heated under reflux in concentrated hydrochloric acid, methylketones (**1610**) were prepared in 24–73% yields (81S130).

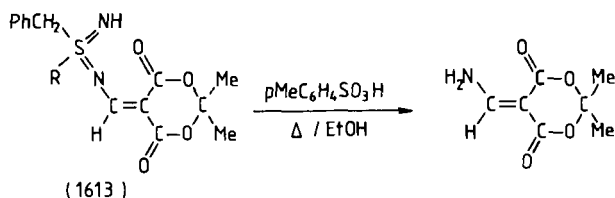


Isopropylidene amino(ethoxycarbonylmethyl)methylenemalonate (**1611**) and boron trifluoride etherate were heated under reflux in ethanol for 48 hr. When the reaction mixture was treated with aqueous potassium carbonate, the triester (**1612**) was obtained in 40% yield, while after evaporation of the solvent and treatment of the residue with water, diethyl 3-oxoglutarate was isolated in 22% yield (81S130).

The ethanolysis of isopropylidene (alkylbenzyliminosulfanylidene)-



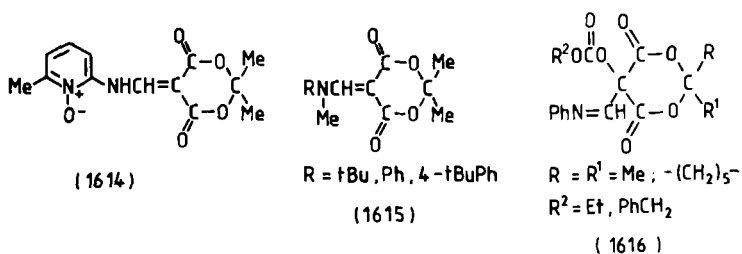
aminomethylenemalonates (**1613**) in boiling ethanol in the presence of *p*-toluenesulfonic acid for 48 hr gave isopropylidene aminomethylenemalonate in 47% yield (88CB805).



3-Chloroperbenzoic acid was gradually added, below 40°C, to a solution of isopropylidene *N*-(6-methyl-2-pyridyl)aminomethylenemalonate in chloroform, and the reaction mixture was then heated on a steam bath for 30 min to yield the *N*-oxide (**1614**) (74USP3856800, 74USP3857851; 75USP3869464, 75USP3873554, 75USP3876650, 75USP3882132).

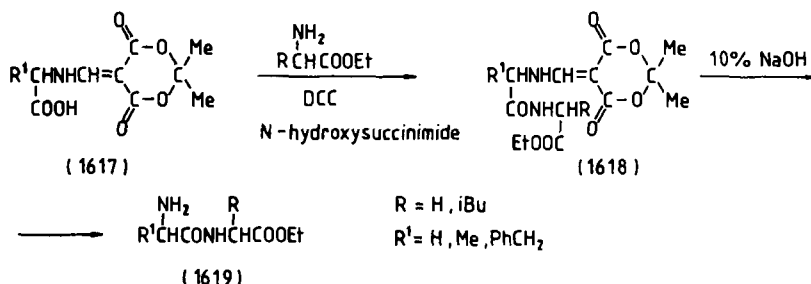
Isopropylidene *N*-substituted aminomethylenemalonates (**442**, $\text{R}^1 = \text{R}^2 = \text{Me}$) were methylated with methyl iodide in dimethyl sulfoxide in the presence of sodium hydride at room temperature overnight to give the *N*-methyl derivatives (**1615**) in 56–90% yields [88JCS(P1)863, 88JCS(P2)759].

Alkylidene phenylaminomethylenemalonates (**444**) were reacted with sodium hydride or lithium hydride in acetonitrile at 40°C for 2 hr. The reaction mixtures were then cooled to 0–20°C, and they were treated with a solution of dialkyl peroxydicarbonate in methylene chloride for 24 hr to give 5-alkoxycarbonyloxy-5-phenyliminomethyl-1,3-dioxane-4,6-diones (**1616**) in 54–75% yields (80CB2630).



The coupling of isopropylidene aminomethylenemalonates (**1617**) with amino acid esters gave the corresponding protected dipeptide (**1618**) in 41–90% yields (85MI3; 86YZ154). Alkaline hydrolysis of the protected dipeptides (**1618**) at room temperature afforded the free dipeptides (**1619**) and isopropylidene hydroxymethylenemalonate (85MI3). Acidic hydrolysis was unsuccessful.

The reaction of isopropylidene piperidinomethylenemalonate and methyl magnesium iodide in a mixture of diethyl ether and THF at room temperature gave isopropylidene ethylenemalonate in 92% yield (88JA1880) (Scheme 58).

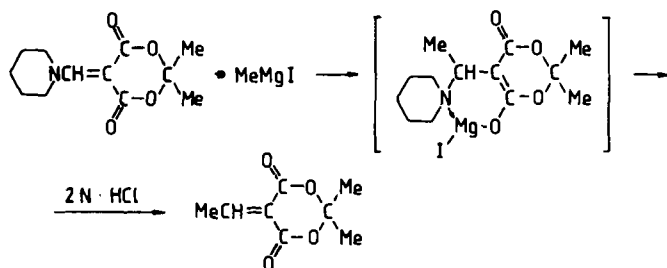


C. Reactions of 2-Azacycloalkyidenemalonates

The treatment of tri(tert-butyl) ester (**511**) with trifluoroacetic acid gave compound **1620** (85CC583).

The heating of isopropylidene (thiazolo[5,4-*d*]thiazolidene)malonate (**496**) in concentrated sulfuric acid at 90°C for 10 min afforded the dimethyl derivative (**1621**) in 92% yield (74UKZ1331).

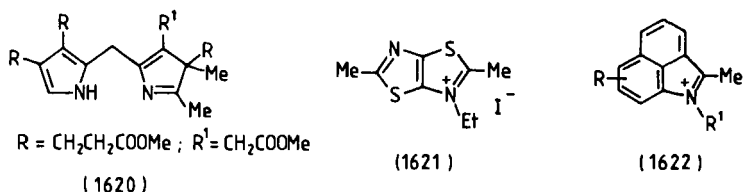
Isopropylidene malonate derivatives (**501**) were boiled in a mixture of



SCHEME 58

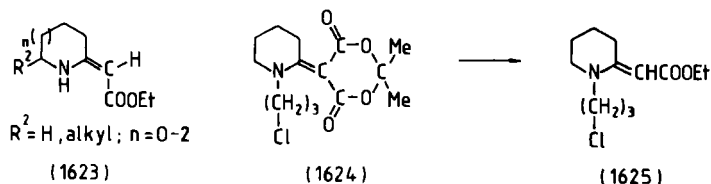
acetic acid and 50% perchloric acid or in hydrochloric acid for 30 min to give 2-methylbenz[*cd*]indole salts (**1622**) 75–96% yields (82ZOR435).

5-Nitro-2-methylpyridine was obtained in 87% yield when diethyl malonate was reacted with 5-nitro-2-chloropyridine in DMF in the presence of sodium hydroxide at room temperature, and the diethyl (5-nitro-2-pyridyl)malonate was then hydrolyzed and decarboxylated by heating in dilute hydrochloric acid at reflux temperature (88GEP3707361, 88GEP3708093).



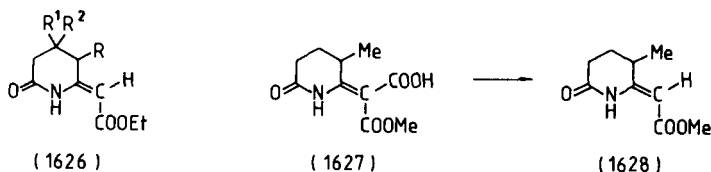
The treatment of isopropylidene (2-azacycloalkylidene)malonates (**468**, $R^4 = \text{H}$) with sodium ethylate in boiling ethanol for 12 hr or overnight gave the amino ester (**1623**) in 58–91% yields (79JOC3089; 88FRP2607497). Acidic and nonacidic alcoholysis was ineffective (79JOC3089).

Isopropylidene [1-(3-chloropropyl)piperidin-2-ylidene]malonate (**1624**) in refluxing ethanol in the presence of boron trifluoride etherate was transformed into ethyl [1-(3-chloropropyl)piperidin-2-ylidene]acetate (**1625**) in 90% yield (87H2335, 89T6161). Similar reaction was also carried out with isopropylidene [1-(2-chloroethyl)pyrrolidin-2-ylidene]malonate (89T6161).

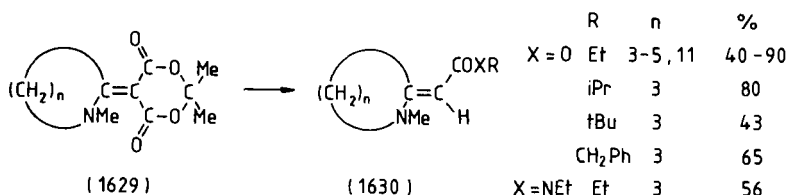


The treatment of isopropylidene (6-oxopiperidin-2-ylidene)malonates (**540**, $n = 1$) with sodium ethylate in boiling ethanol overnight afforded ethyl (6-oxopiperidin-2-ylidene)acetates (**1626**), with *Z* configuration, in 39–73% yields (81TL2255).

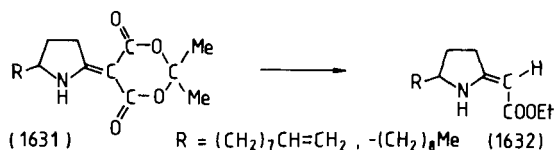
A methanolic solution of isopropylidene (3-methyl-6-oxopiperidin-2-ylidene)malonate (**537**) was boiled overnight in the presence of sodium methylate to give monomethyl malonate (**1627**) in 86% yield (86JST319). The half ester (**1627**) was decarboxylated at 150°C to afford methyl (3-methyl-6-oxopiperidin-2-ylidene)acetate (**1628**) in 95% yield.



Ethanollic solutions of isopropylidene (azacycloalk-2-ylidene)malonates (**1629**) were boiled in the presence of sodium ethylate overnight to give ethyl (azacycloalk-2-ylidene)acetates (**1630**, $XR = OEt$) in 56–90% yields (83S195). Acrylates (**1630**, $X = O$) or acryl amides (**1630**, $X = NEt$) were also prepared when mixtures of cyclic esters (**1629**) and the respective alcohol or amine were heated for 30 min at a temperature $25^\circ C$ higher than the decomposition point. The latter was sometimes carried out in acetone.



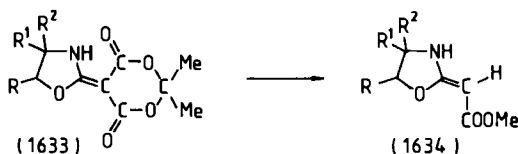
The heating of ethanolic solutions of isopropylidene (2-pyrrolidinyli-dene)malonates (**1631**) in an autoclave at $230^\circ C$ for 30 min afforded ethyl (2-pyrrolidinyli-dene)acetates (**1632**) in 60–62% yields (88FRP2607497, 88TL3061).



The treatment of isopropylidene (1,3-oxazol-2-ylidene)malonates (**1633**) with methanol at $120^\circ C$ gave methyl (1,3-oxazol-2-ylidene)acetates (**1634**) in 14–49% yields (86JHC701).

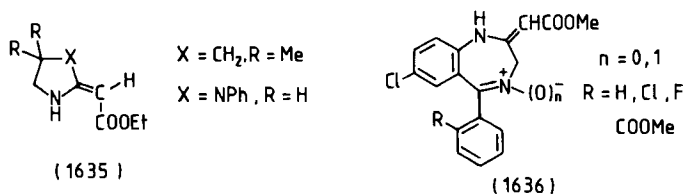
The heating of (2-pyrrolidinyli-dene)- and (2-imidazolidinyli-dene)malonates (**534**, $X = CH_2$, $R = Me$; $X = NPh$, $R = H$) in boiling ethanol in the presence of sodium ethylate for 8 hr gave the corresponding acetate (**1635**) (88AP429).

(1,4-Benzodiazepin-2-ylidene)malonates (**503**) were heated in boiling methanol in the presence of sodium hydroxide or potassium hydroxide

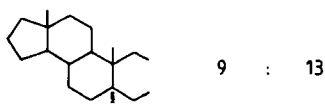
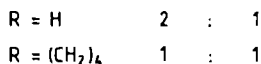
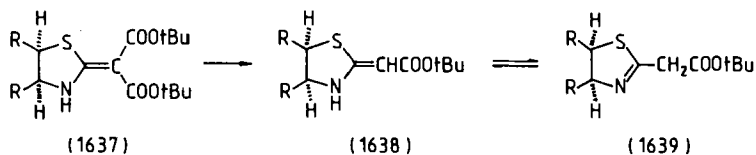


under nitrogen for 3–5 hr to give (1,4-benzodiazepin-2-ylidene)acetates (**1636**) (83USP4401597).

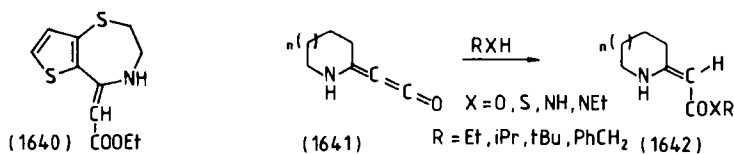
Di-*tert*-butyl 2-thiazolylidenemalonates (**1637**) were treated with trifluoroacetic acid in methylene chloride at ambient temperature for 30–40 min to afford equilibrium mixtures of (thiazol-2-ylidene)acetates (**1638**) and (thiazolin-2-yl)acetates (**1639**) in 82–100% yields (85AJC745).



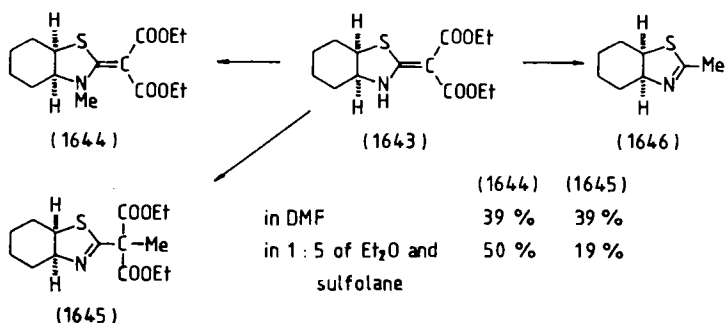
An ethanolic solution of diethyl thieno[2,3-*f*]-1,4-thiazepin-5(2*H*)-ylidene malonate (**515**) was refluxed in the presence of sodium ethylate. The reaction mixture was then evaporated, and the residue was treated with water to give (thieno[2,3-*f*]-1,4-thiazepin-5-ylidene) acetate (**1640**) (86EUP183994).



The thermolysis of isopropylidene 2-azacycloalkylidenemalonates (**468**, R² = R⁴ = H, *n* = 0–2) gave unstable ketenes (**1641**), which were reacted with alcohols, thiols, and protic amines to afford *Z*-enamino ester derivatives (**1642**) in 63–98% yields (81TL963).



The reduction of diethyl (*cis*-octahydrobenzothiazol-2-ylidene)malonate (**1643**) with aluminum amalgam, sodium borohydride, tris(triphenylphosphine)rhodium(I) chloride, $[RhCl(pyridine)_2(HCONMe_2)(BH_4)]^+Cl^-$ and diimide were unsuccessful (85AJC745). The reaction of diethyl (*cis*-octahydrobenzothiazol-2-ylidene)malonate (**1643**) and methyl iodide in diethyl ether or in ethanol in the presence of sodium hydride at room temperature for 4 days gave the *N*-methyl derivative (**1644**) in 45% and 29% yields, respectively. When the reaction was carried out in DMF or in a 1 : 5 mixture of diethyl ether and sulfolane, mixtures of *N*-methyl (**1644**) and *C*-methyl (**1645**) derivatives were obtained. The treatment of diethyl (*cis*-octahydrobenzothiazol-2-ylidene)malonate (**1643**) with potassium hydroxide in boiling ethanol for 4 hr gave 2-methyl-*cis*-octahydrobenzothiazole (**1646**) (85AJC745).

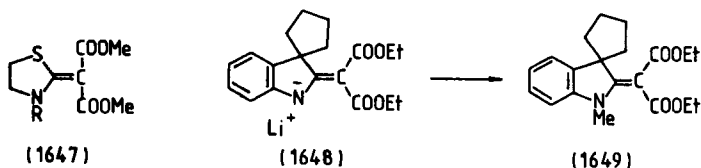


Diethyl (4,4-dimethyl-2-pyrrolidinylidene)malonate (**534**, $X = CMe_2$) was *N*-methylated with dimethyl sulfate, in THF in the presence of potassium *tert*-butylate, in 75% yield (88AP429).

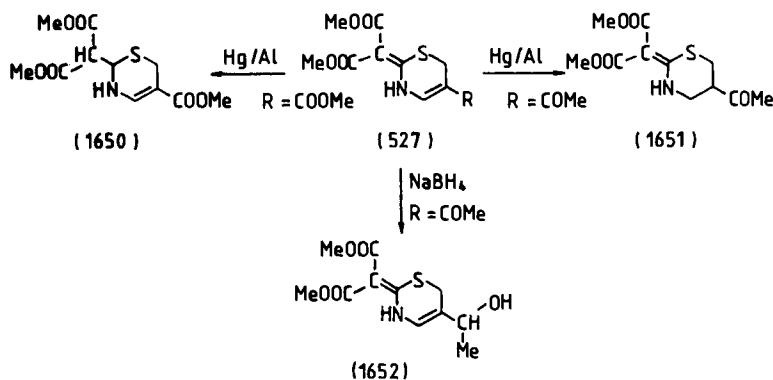
2-Thiazolidinylidenemalonate (**1647**, $R = H$) was alkylated with dimethyl sulfate in boiling acetone in the presence of potassium carbonate for 20 hr to afford (3-methylthiazolidin-2-ylidene)malonate (**1647**, $R = Me$) in 86% yield (69T4649).

The lithium salt (**1648**) of the spiro malonate (**550**) was methylated with methyl iodide in a mixture of THF and DMF at 20°C for 60 hr to give the *N*-methyl derivative (**1649**) in 58% yield (78JOC3702).

The exocyclic double bond of (tetrahydro-1,3-thiazin-2-ylidene)malonate (**527**) was saturated by reduction with Hg/Al in methanol at ambient



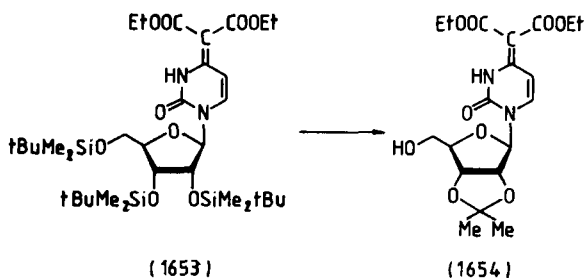
temperature for 1 hr, when the 1,3-thiazine contained a methoxycarbonyl group at position 5. However, the *endo* cyclic double bond was hydrogenated when it bore an acetyl group at position 5 to give (tetrahydro-1,3-thiazin-2-yl)malonate (**1650**) and (hexahydro-1,3-thiazin-2-ylidene) malonate (**1651**) in 84% and 62% yields, respectively [83PS(15)143]. The reaction of the 5-acetyl derivative (**527**, R = COMe) with sodium borohydride in boiling methanol for 30 min led to reduction of the acetyl group, to afford the 5-(1-hydroxyethyl) derivative (**1652**) in near quantitative yield [83PS(15)143].



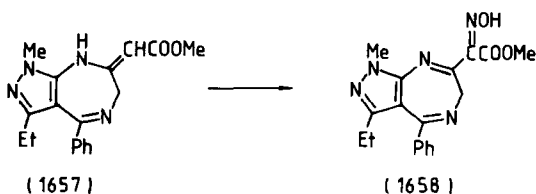
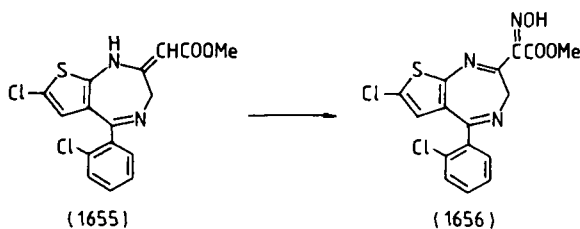
The *N*-oxide of (1,4-benzodiazepin-2-ylidene)malonate (**503**, R = H, *n* = 1) was deoxygenated by catalytic hydrogenation over Raney Nickel in a mixture of methanol and THF at atmospheric pressure for 5 hr (83USP4401597) and by treatment with phosphorus trichloride in methylene chloride at ambient temperature overnight (75JOC153; 83USP-4401597).

4-Pyrimidinylidenemalonate (**1653**) was converted into the isopropylidene derivative (**1654**) in 70% yield by treatment with the boron trifluoride methanol complex in methylene chloride and then with 2,2-dimethoxypropane (87TL2821).

(Thieno[2,3-*e*]diazepinylidene)malonate (**506**, R = H, R¹ = 2-ClPh, X = CCl, Y = S) was heated in boiling methanol in the presence of pot-



assium hydroxide for 3 hr under nitrogen; the solvent was evaporated, the residue was dissolved in methylene chloride, and the solution was treated with aqueous sodium bicarbonate. The organic layer was evaporated; the residue was dissolved in glacial acetic acid and treated with sodium nitrite at ambient temperature to give thieno[2,3-*e*]diazepine-2-acetate (**1656**) via **1655** (83USP4401597).



(Pyrazolo[3,4-*e*]diazepin-2-ylidene)malonate (**506**, R = Et, R¹ = Ph, X = N, Y = NMe) afforded pyrazolodiazepine-2-acetate (**1658**) via **1657** under similar conditions (83USP4401597).

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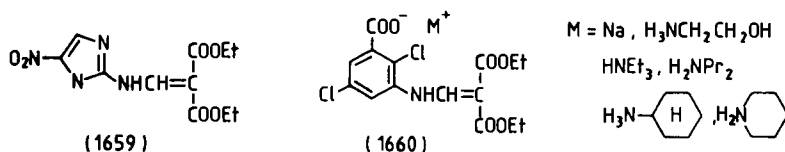
Appendix

A. Miscellaneous Methods

The antiamebic activities of 2-imidazolylaminomethylenemalonate (**1659**) were investigated via *in vitro* and *in vivo* tests [84IJC(B)342].

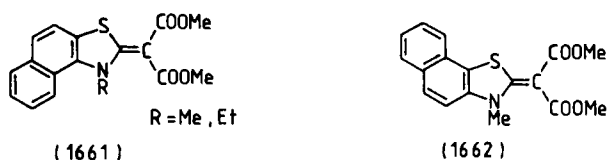
Insecticidal activity of diethyl *N*-(4-chloro-2-methylphenyl)aminomethylenemalonate was investigated against American and German cockroaches (86MI7).

Different salts of phenylaminomethylenemalonate (**1660**) were prepared in water (77GEP2553788).

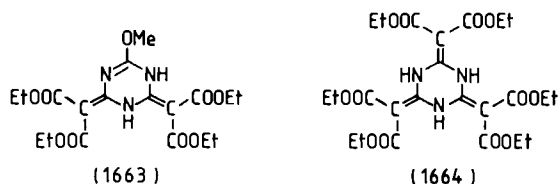


The sodium salt of the phenylglycine derivative (**33**) was investigated as an absorption promoter for the rectal absorption of beta-lactam antibiotics and insulin [80JAP(K)31040; 81CPB1998, 81CPB2012].

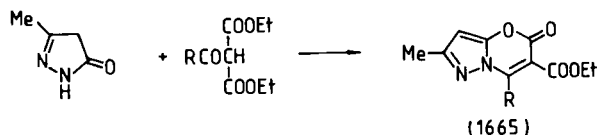
(Naphthothiazol-2-ylidene)malonates (**1661** and **1662**) were applied in silver halide photographic emulsions as sensitizer dyes [82JAP(K)54936].



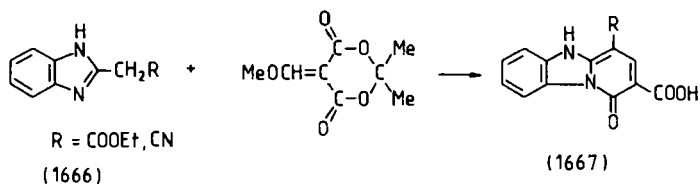
The antibradykinin activities of malonates (**1663** and **1664**) were investigated (81KFZ50).



The reaction of 3-methyl-5-pyrazolone with diethyl 2-acylmalonates at 140–150°C for 2 hr afforded pyrazolo[5,1-*b*]oxazine-6-carboxylates (**1665**) in 22–64% yields [77JAP(K)77089].

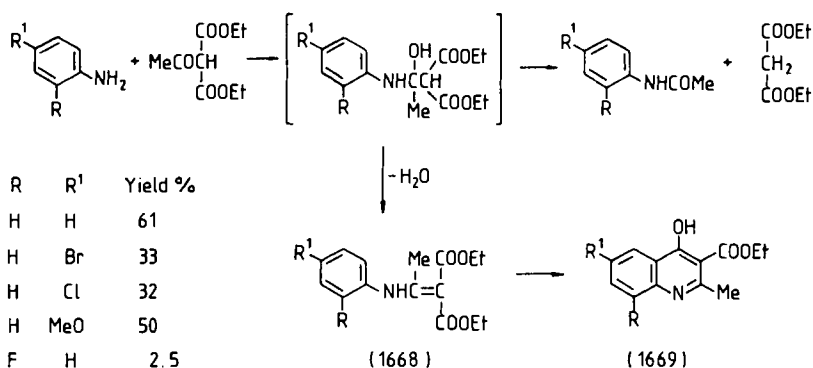


When the reactions were carried out in chloroform for 2 hr, isopropylidene methoxymethylenemalonate reacted on the active methylene group of 2-benzimidazolylacetate and acetonitrile (**1666**) in the first step, and in the next step, one of the ring nitrogens was involved in a cyclization to give pyrido[1,2-*a*]benzimidazole-2-carboxylic acids (**1667**) in 86–89% yields (88YZ856).



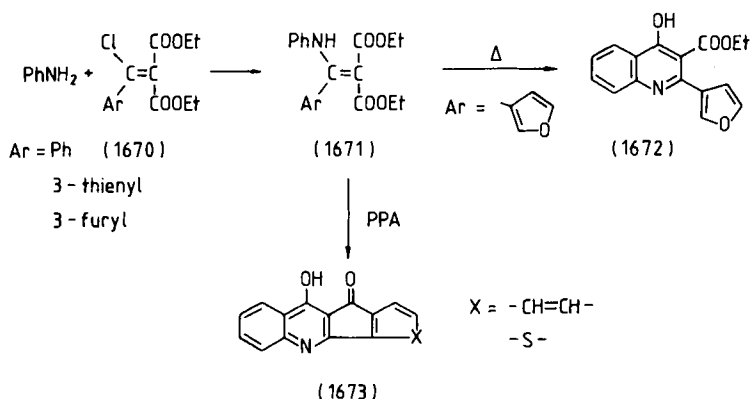
B. Recent Research

Ethyl 4-hydroxy-2-methylquinoline-3-carboxylates (**1669**) were prepared in 3–61% yields when anilines and diethyl acetylmalonate were heated in the presence of a few drops of concentrated hydrochloric acid at 45–55°C for 16 hr *in vacuo* (20–100 mm Hg). The temperature of the reaction mixtures was then raised to 190–200°C, and the reaction mixtures were stirred at this temperature for 0.5 hr (88KGS931). From the mother liquors, 1-(arylamino)ethylidenemalonates (**1668**) could also be isolated. When the starting materials were reacted in boiling benzene in the presence of hydrochloric acid, the quantities of water and malonate formed were determined. Kononov *et al.* concluded from their results that the reaction pathways depended on the basicity of the anilines: if the pK_a value of the amine was lower than 3, the starting materials practically did not react with the acetyl group of the acetylmalonate. When the pK_a value of the amine lay in the range 4.5–5.5, the formation of 1-anilinoethylidenemalonate (**1668**) predominated, while with pK_a above 5.5, that of the acetanilide was favored. Thus, the aminopyridines afforded only acetamidopyridines



instead of the corresponding diethyl 1-(pyridylamino)ethylidenemalonates or 2-methylnaphthyridine-3-carboxylates.

Diethyl aryl(chloro)methylenemalonates (**1670**) were reacted with aniline in the presence of triethylamine at 90°C for 12 hr to give aryl(phenylamino)methylenemalonates (**1671**) in 57–66% yields (90JOC2513). The thermal cyclization of compound **1671** (Ar = 3-furyl) at 250°C gave quinolinecarboxylate (**1672**) in 85% yield. The cyclizations of compounds **1671** (Pr = Ph, 3-thienyl) in polyphosphoric acid at 210–230°C for 5 min afforded tetracyclic derivatives (**1673**) in 50–75% yields.

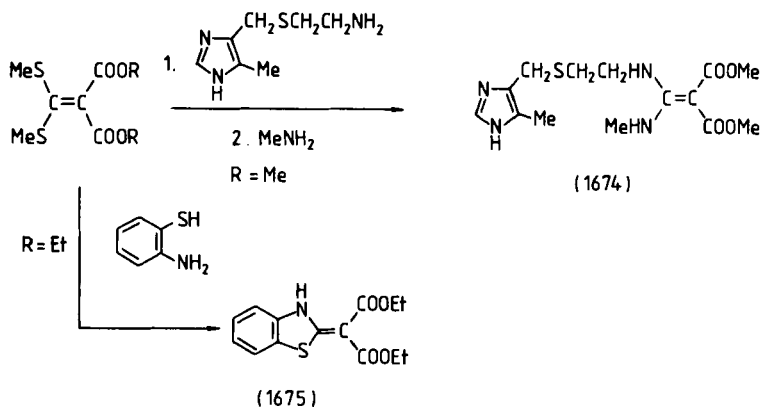


Diethyl malonate was reacted with 2,3,4-trifluorophenyl isothiocyanate in the presence of sodium hydride in THF at 5–10°C for 40 min, and then at ambient temperature for 105 min, to give the sodium salt of diethyl (2,3,4-trifluorophenylamino)(mercapto)methylenemalonate. The latter was then treated with 1-acetoxy-3-chloroacetone or *p*-methoxybenzyl

chloride in DMF at room temperature for 30–60 min to afford diethyl (2,3,4-trifluorophenylamino)(3-acetoxy-2-oxopropylthio)- and (*p*-methoxybenzylthio)methylenemalonates in 89% and 94% yields, respectively (88EUP286089).

Dimethyl bis(methylthio)methylenemalonate was reacted with 4-[(2-aminoethylmercapto)methyl]-5-methylimidazole in ethanol and then with methylamine to give bisaminomethylenemalonate (**1674**) in 15% yield (82AP680).

Diethyl benzothiazol-2-ylidenemalonate (**1675**) was prepared in the reaction of diethyl bis(methylthio)methylenemalonate and 2-aminothiophenol in boiling ethanol for 16 hr in 78% yield (90CB541).

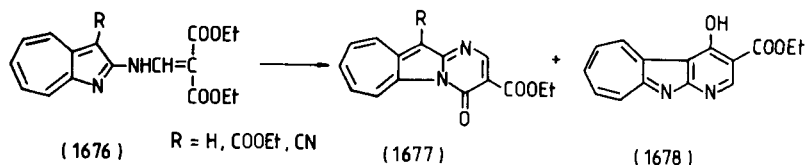


Cyclization of diethyl *N*-[cyclohepta(*b*)pyrrol-2-yl]aminomethylene-malonates (**1676**), by heating in xylene, *t*-butylbenzene, or tetralin at reflux temperature, gave cyclohepta[4,5]pyrrolo[1,2-*a*]pyrimidine-3-carboxylates (**1677**) in 46–90% yields (87BCJ1053). Cyclization were also carried out in a mixture of phosphoryl chloride and polyphosphoric acid. While compound **1676** ($\text{R} = \text{COOEt}$) gave **1677** ($\text{R} = \text{COOEt}$) in 95% yield, the unsubstituted **1676** ($\text{R} = \text{H}$) afforded a mixture of **1677** ($\text{R} = \text{H}$) and 4-hydroxycyclohepta[4,5]pyrrolo[2,3-*b*]pyridine-3-carboxylate (**1678**) in 7% and 48% yields, respectively. The nitrogen bridgehead compound (**1677**, $\text{R} = \text{H}$) could not be transformed into pyridine derivative (**1678**).

Insecticidal activity of dialkyl [(diethoxyphosphinyl) (dialkylamino)-methylene]malonates was investigated against aspid and flies (84MI3).

Some carbon-13-proton spin coupling constants of dimethyl *N,N*-dimethylaminomethylenemalonate were determined (90IZV356).

The crystal structure of isopropylidene *N,N*-dimethylaminomethylene-

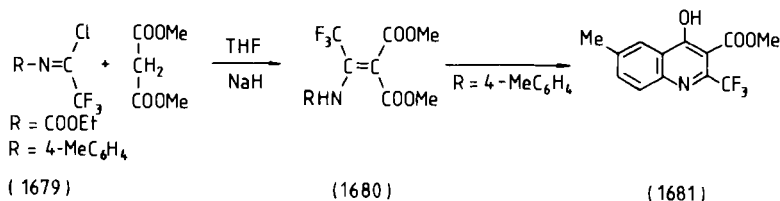


malonate was determined in an X-ray crystallographic study [89-JCR(S)118].

Diethyl *N,N*-dimethylaminomethylenemalonate was obtained in the reaction of di-*tert*-butyl[bis(dimethylamino)methyl]phosphine and diethyl malonate at 80–100°C for 1 hr in 45% yield (88ZOB1445; 89ZOB2206).

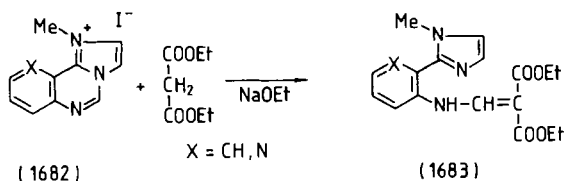
The amino group of alkenamides was reacted with EMME at 140–160°C (89EUP302016).

Imidoyl chlorides (**1679**) were reacted with dimethyl malonate in THF in the presence of sodium hydride at room temperature to give aminomethylenemalonates (**1680**) in 67–82% yields (89TL4821). The 4-methylphenyl derivative of **1680** ($R = 4\text{-MeC}_6\text{H}_4$) was cyclized by heating in cumene at 200°C to afford 4-hydroxy-2-trifluoromethylquinoline-3-carboxylate (**1681**) in 66% yield.



Diethyl *N*-[2,4-bis(dimethylamino)-1,3,5-triazin-6-yl]aminomethylene-malonate was prepared in the reaction of 2,4-bis(dimethylamino)-6-isocyano-1,3,5-triazine and diethyl malonate in boiling benzene in the presence of copper(I) chloride for 4 hr in 83% yield (89JHC901).

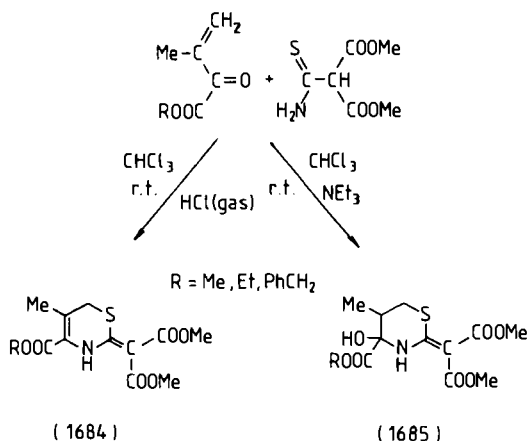
The treatment of quaternary salts (**1682**) with diethyl malonate in the



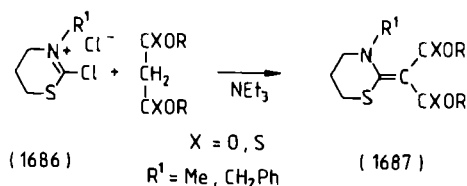
presence of sodium ethylate in ethanol at ambient temperature gave amino-methylenemalonates (**1683**) in 60–71% yields (89M269).

The reaction of 3-methyl-2-oxo-3-butenates and dimethyl (aminothiocarbonyl)malonate afforded (dihydro-1,3-thiazin-2-ylidene)malonate (**1684**) under acidic conditions, while in the presence of triethylamine, (tetrahydro-1,3-thiazin-2-ylidene)malonates (**1685**) were the products (88SC1043).

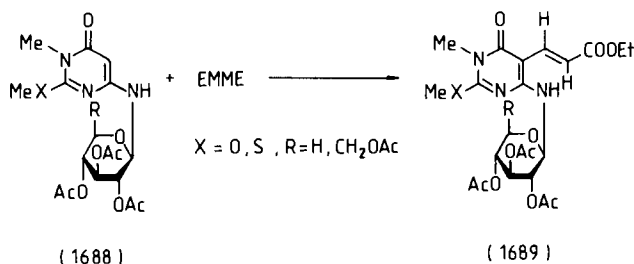
The reaction of diethyl and isopropylidene [mercapto(phenylamino)-methylene]malonates and 3,3-pentamethylenoxaziridine in toluene afforded the appropriate (3,3-pentamethylene-1,2,4-thiadiazolidin-5-ylidene)malonates(89EGP270910).



Dialkyl and isopropylidene malonates were reacted with 2-chloro-1,3-thiazinium chlorides (**1686**) in methylene chloride in the presence of triethylamine to give (1,3-thiazin-2-ylidene)malonates (**1687**) in 5–13% yields (89AP593, 89GEP3803783).



Instead of the amino group, the ring carbon 5 of the 6-glycosylaminopyrimidines (**1688**) was involved in the reaction with EMME in boiling acetic acid for 10–24 hr to give the corresponding (*E*)-5-(2-ethoxycarbonylvinyl) derivatives (**1689**) in 12–25% yields (88H2439).



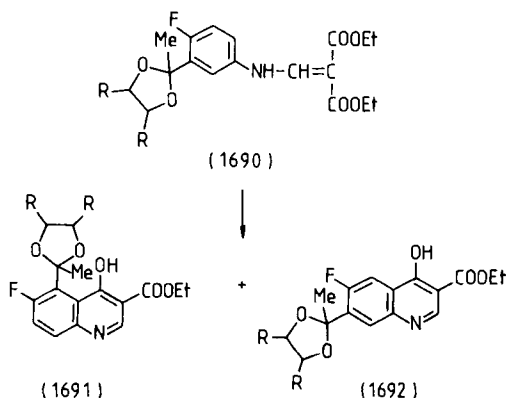
The reaction of diethyl acetyl- and propionylmalonates with hydroxylamine hydrochloride or its *N*-methyl derivative in ethanol afforded the appropriate ethyl 3-alkyl-2,5-dihydro-5-oxo-4-isoxazolecarboxylate (88-TL6339).

Ethyl 3-methyl-5-oxopyrazoline-4-carboxylate and its 1-methyl derivative were prepared in the reaction of diethyl acetylmalonate and hydrazine hydrate, and methylhydrazine in acetic acid at 95–100°C for 3 hr in 83% and 95% yields, respectively (89SC2087).

The heating of diethyl 2-(2,4,6-trichlorophenyl)hydrazino methylenemalonate, prepared from 2,4,6-trichlorophenylhydrazine and EMME in ethanol at –10°C, gave ethyl 1-(2,4,6-trichlorophenyl)-5-hydroxypyrazole-4-carboxylate at 170–175°C for 45 min in 82% yield (89USP4804398).

The reaction of 2-pyridylhydrazine and EMME in diphenyl ether at 190°C for 30 min give ethyl 5-hydroxy-1-(2-pyridyl)pyrazole-4-carboxylate in 6% yield (89MI435).

The thermal cyclization of *N*-[4-fluoro-3-(2-methyl-1,3-dioxolan-2-yl)-phenyl]aminomethylenemalonate (**1690**, *R* = *H*) in Dowtherm A at 250°C for 2.5–3 hr afforded a 1 : 1 mixture of the isomeric 5- and 7-substituted 4-hydroxyquinoline-3-carboxylates (**1691** and **1692**, *R* = *H*) (90JMC1246).



When the 2,4,5-trimethyl-1,3,-dioxolane derivative (**1690**, R = Me) was cyclized, then a 1 : 9 mixture of 5- and 7-substituted quinolinecarboxylates (**1691** and **1692**, R = Me) was obtained.

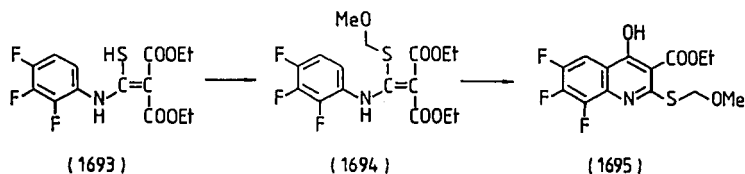
Potassium salt of ethyl 7-chloro-6-fluoro-4-hydroxyquinoline-3-carboxylate (**759**, R = Cl, R¹ = F) was isolated in pure form from a mixture of isomeric ethyl 5-chloro-6-fluoro- and 7-chloro-6-fluoro-4-hydroxyquinoline-3-carboxylates (**758** and **759**, R = Cl, R¹ = F) by heating in DMF in the presence of an excess of potassium carbonate (89USP4868305).

The heating of diethyl *N*-(3-hydroxy-2-methoxyphenyl)aminomethylenemalonate in boiling diphenyl ether in the presence of water afforded decarboxylated 4,7-dihydroxy-8-methoxyquinoline in 61% yield (89MI5).

Regioselective cyclization of *N*-(4-benzoyl-5-benzimidazolyl)aminomethylenemalonates (**969**, R = H, Me) was observed. When the cyclization was carried out in polyphosphoric acid, then 4-phenylimidazo[4,5-*f*]quinoline-5-carboxylates (**970**) were obtained, while the thermal cyclization in diphenyl ether at 200°C, or the cyclization in a mixture of phosphoryl chloride and polyphosphoric acid afforded 4-benzoyl-8-hydroxyimidazo[5,4-*g*]quinoline-7-carboxylates (**971**) (89KFZ692).

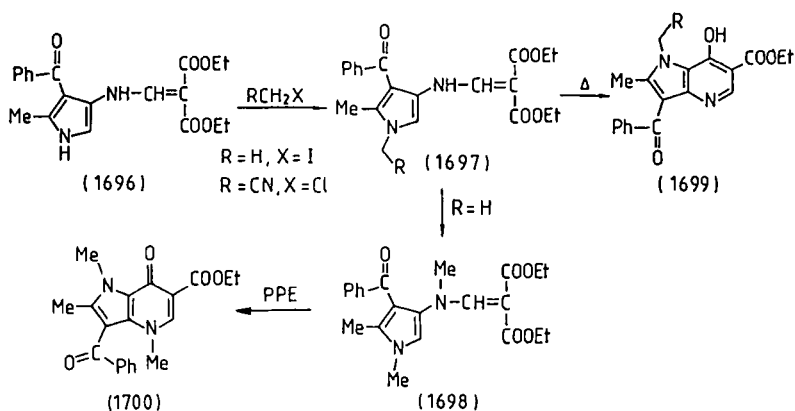
Cyclization of dialkyl *N*-(4-substituted or 2-substituted 3-thienyl)aminomethylenemalonates in phosphoryl chloride yielded the corresponding 3-substituted 7-chlorothieno[3,2-*b*]pyridine-6-carboxylate (89MIP1), or 1-substituted-4-chlorothieno[3,4-*b*]pyridine-5-carboxylate, respectively, [89JCR(S)196].

2,3,4-Trifluorophenyl isothiocyanate was reacted with diethyl malonate in THF in the presence of sodium hydride at ambient temperature for 1 hr to give diethyl mercapto[(2,3,4-trifluorophenyl)amino]methylenemalonate (**1693**). The latter was alkylated with chloromethyl methyl ether in the presence of triethylamine (89EUP315827). Aminomethylenemalonate (**1694**) was cyclized by heating in diphenyl ether at 230°C for 15 min to yield quinoline-3-carboxylate (**1695**).



3-(Cyanomethylamino)-1-phenyl-2-buten-1-one was cyclized in an exothermic reaction in ethanol in the presence of sodium ethylate. Then the reaction mixture was treated with mol. equiv. of acetic acid and EMME to

give 3-pyrrolylaminomethylenemalonate (**1696**) in 81% yield (90JHC1201). The pyrrole nitrogen of **1696** was alkylated by methyl iodide in DMF in the presence of potassium tert-butyrate, and by chloroacetonitrile in THF in the presence of sodium hydride at room temperature to give (1-substituted 3-pyrrolyl)aminomethylenemalonates (**1697**) in 86% and 84% yields, respectively. The amino group of **1697** ($R = H$) was alkylated with dimethyl sulfate in boiling THF in the presence of sodium hydride overnight to give 3-pyrrolylaminomethylenemalonate (**1698**). Aminomethylenemalonates (**1697**) were cyclized by heating in boiling Dowtherm A to give 7-hydroxypyrrolo[3,2-*b*]pyridine-6-carboxylates (**1699**). 7-oxo-4,7-Dihydropyrrolo[3,2-*b*]pyridine-3-carboxylate (**1700**) was obtained by the ring closure of 3-pyrrolylaminomethylenemalonate (**1698**) by heating in polyphosphate at 90°C for 75 min.

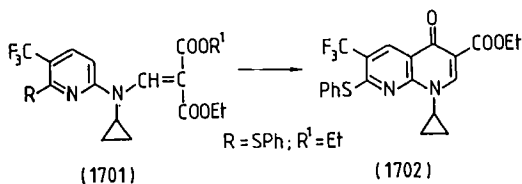


Diethyl *N*-cyclopropyl(6-chloro-5-trifluoromethyl-2-pyridinyl)aminomethylenemalonate (**1701**, $R = Cl$, $R^1 = Et$) was obtained in the reaction of sodium salt of diethyl cyclopropylaminomethylenemalonate and 2,6-dichloro-3-trifluoromethylpyridine in dimethyl sulfoxide at 50°C for 4 hr in 86% yield (90JHC1527). When **1701** ($R = Cl$, $R^1 = Et$) was reacted with ethoxycarbonylpiperazine in dimethyl sulfoxide at 100°C for 16 hr, then a 1:1 mixture of 2-pyridylaminomethylenemalonate (**1701**, $R = 4$ -ethoxycarbonylpiperazinyl, $R^1 = Et$) and 2-(cyclopropylamino)-6-chloro-5-trifluoromethylpyridine were obtained in 40% yield. However, the 6-phenylthio derivative (**1701**, $R = SPh$, $R^1 = Et$) was prepared in high yield in the reaction of the 6-chloro derivative (**1701**, $R = Cl$, $R^1 = Et$) and sodium phenylsulfide in dimethyl sulfoxide at ambient temperature for 2.5 hr.

The ring closure of *N*-cyclopropyl-*N*-(2-pyridyl)aminomethylenemalonates (**1701**, $R = Cl, SPh$, $R^1 = Et$) were investigated in a mixture of acetic

anhydride and concentrated sulfuric acid at 60–110°C (90JHC1527). In the case of 6-chloro derivative (**1701**, R = Cl, R¹ = Et), only a mixture of hydrogen, ethyl 2-pyridylaminomethylenemalonates (**1701**, R = Cl and OH, R¹ = H), was obtained. The 6-phenylthio derivative (**1701**, R = SPh, R¹ = Et) afforded 1,8-naphthyridine-3-carboxylate (**1702**) in 45% yield.

Diethyl (1,4-benzothiazin-4-yl)methylenemalonates were cyclized to pyrido[1,2,3-*de*]-[1,4]benzothiazine-6-carboxylates by heating in a mixture of acetic acid and concentrated sulfuric acid or in polyphosphoric acid (89EUP310969).



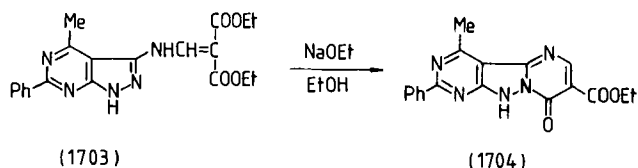
The ring closure of (1,2,3,4-tetrahydroquinolin-1-yl)methylenemalonate was achieved by heating in polyphosphoric acid (89EUP323189).

N-cyclopropyl- and *N*-ethyl-*N*-(substituted phenyl)aminomethylenemalonates were cyclized in polyphosphoric acid [89EUP332033, 89JAP(K)83068], in ethyl polyphosphate (89USP479490), and in phosphoryl chloride (89EUP304158).

Ethyl 2-(3-pyridyl)-7-hydroxy-1,2,4-triazolo[1,5-*a*]pyrimidine-6-carboxylate was obtained in the reaction of 3-amino-5-(3-pyridyl)-1,2,4-triazole and EMME in boiling acetic acid for 4 hr in 22% yield [89IJC(B)242].

The reaction of diethyl 1-ethoxyethylidenemalonate and an 3-amino-1,2,4-triazole derivative yielded an ethyl 7-methyl-5-oxo-1,5-dihydro-1,3,4-triazolo[4,3-*a*]pyrimidine-6-carboxylate [88JAP(K)246739].

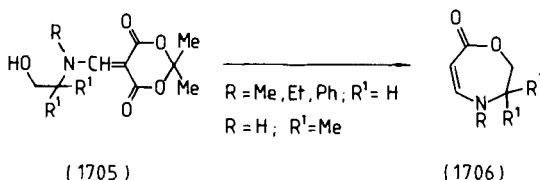
N-(Pyrazolo[3,4-*d*]pyrimidin-3-yl)aminomethylenemalonate (**1703**) was cyclized in ethanol in the presence of sodium ethylate to yield pyrazolo[5,4-*d*:2,3-*a*]dipyrimidine-7-carboxylate (**1704**) [89JCR(S)333].



The thermal cyclization of isopropylidene *N*-(2-unsubstituted 4-pyrimidinyl)aminomethylenemalonates gave 4*H*-pyrimido[1,6-*a*]pyrimidin-4-ones (90JMC1963), while that of isopropylidene (2-substituted 4-pyrimidinyl)aminomethylenemalonates afforded 5-hydroxypyrido[2,3-*d*]pyrimidines (90SL549).

Flumequine was prepared when 6-fluoro-2-methyl-1,2,3,4-tetrahydroquinoline was first reacted with alkylidene malonates and trimethyl orthoformate in THF in the presence of *p*-toluenesulfonic acid, and then the products, alkylidene (6-fluoro-2-methyl-1,2,3,4-tetrahydroquinolin-1-yl) methylenemalonates, were cyclized in xylene on the action of polyphosphoric acid or ethyl polyphosphate at 110–115°C for 1 hr (89EUP310849).

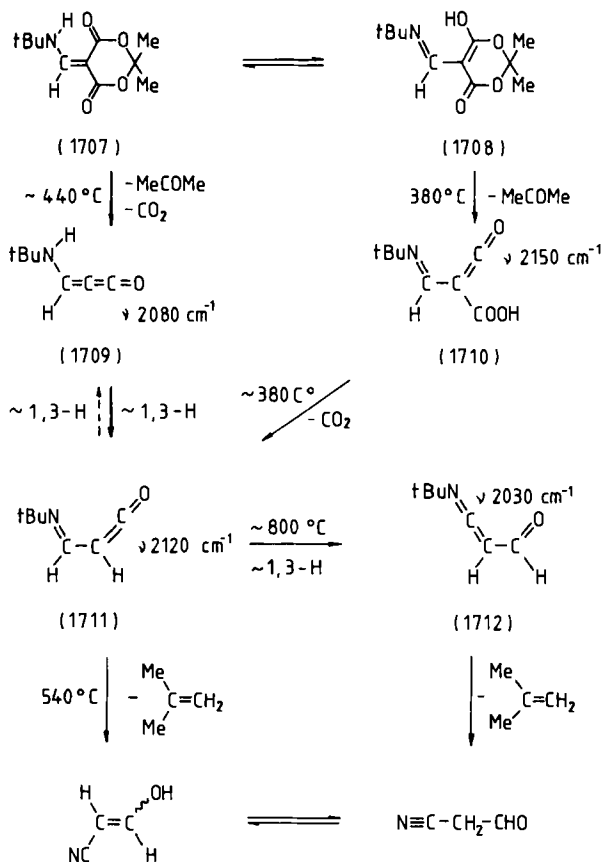
The gas-phase thermolysis of isopropylidene *N*-(2-hydroxyethyl)aminomethylenemalonates (**1705**), prepared from the appropriate 2-hydroxyethylamines and isopropylidene ethoxymethylenemalonate (**422**), gave 1,4-oxazepinones (**1706**) in 47–70% yields (89BSF657). When a phenyl ring was also present on the amino group of the *N*-(2-hydroxyethyl)aminomethylenemalonate (**1705**, R = Ph), the hydroxyl group of the ethyl chain was again involved in the cyclization to give **1706** (R = Ph). If the hydroxy group is on a phenyl ring, i.e. isopropylidene *N*-(2-hydroxyphenyl)aminomethylenemalonate was the starting material, then 4,8-dihydroxyquinoline was the product instead of the appropriate benzo[*b*][1,4]-oxazepinone.



Recently Chuche, Pommelet, Wentrup and their co-workers reported the investigation of syntheses and flash vacuum thermolyses of isopropylidene alkylaminomethylenemalonates (**1707**, **1713**, **1716**, and **1722**) (91-JOC9709).

Thermolysis (550–650°C/10⁻⁴–10⁻⁵ Torr) of *tert*-butylaminomethylenemalonate (**1707**) gave a tautomeric equilibrium of (*Z/E*)-3-hydroxypropenenitrile and cyanoatetaldehyde (see Scheme 59). The products of thermolysis of **1707** were investigated by IR spectroscopy at 77° K using a special apparatus.

At a pyrolysis temperature of 380–440°C the formation of two ketenes (**1710** and **1711**) was detected. The carboxy(imido)ketene (**1710**) was



SCHEME 59

stable to -75°C on warm up, while the imidoyleketene (**1711**) was stable to -120°C . It was suggested that the carboxy(imido)ketene (**1710**) derived from the enol tautomer (**1708**) of **1707** by the elimination of acetone. At a higher pyrolysis temperature (440°C) the appearance of a methyleneketene (**1709**) (stable to -150°C), formed from **1707** by concerted elimination of acetone and carbon dioxide, could be also observed. In another experiment, starting from ethyl 3-(*tert*-butylamino)acrylate between $750\text{--}850^\circ\text{C}$, a sign of ketene imine (**1712**) appeared in IR spectra. This high-temperature formation of ketene imine (**1712**) from iminoketene (**1711**) by 1,3-hydrogen shift is in keeping with the earlier experiments which indicated that this type of 1,3-hydrogen migration possessed a relatively high activation energy.

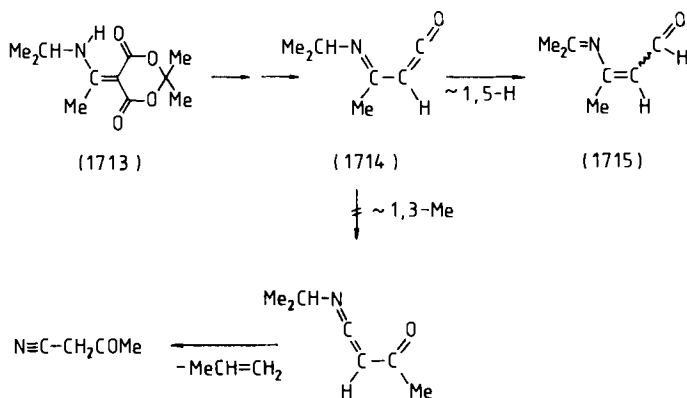
The flash vacuum thermolysis of 1-(isopropylamino)methylenemalonate (**1713**) at 600°C yielded iminoacrolein (**1715**) via imidoylketene (**1714**). 1,3-Methyl migration, similar to 1,3-hydrogen shift between **1711** and **1712**, could not be detected giving cyanoacetone by elimination of propene (see Scheme 60).

The flash vacuum thermolyses (600°C) of (disubstituted methylene)-malonates (**1716**) yielded cyanothioacetates and cyanoacetamides, respectively (**1720**, $R^1 = \text{SMe}$ and NHPr , NHtBu , NMe_2), besides acetone, carbon dioxide, and isobutene or propene (see Scheme 61). In these cases the imidoylketene-to-acylketene imine rearrangement (**1717** \rightarrow **1718** or **1719** \rightarrow **1720**) was facilitated by the presence of an electron-rich methylthio or alkylamino group ($R^1 = \text{SMe}$ and NHPr , NHtBu , NMe_2).

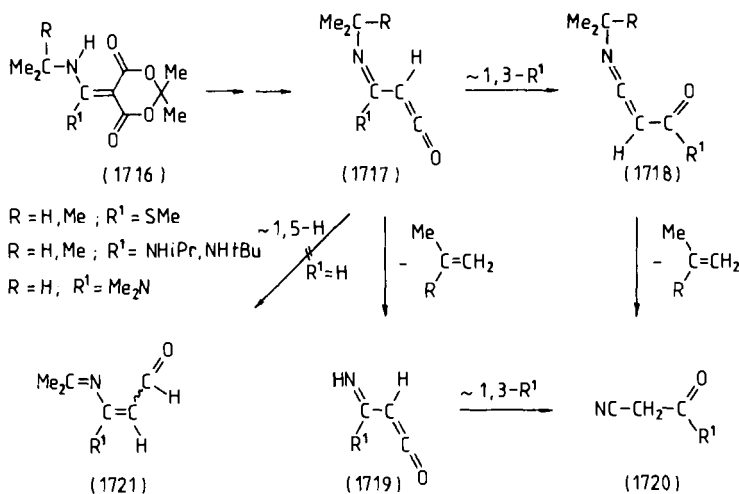
At the thermolyses of isopropylamino derivatives (**1716**, $R = \text{H}$), the formation of iminoacroleins (**1721**) $R^1 = \text{NHPr}$, NMe_2) was not observed from the intermediates **1717** ($R = \text{H}$) by 1,5-hydrogen shift analogues to **1714** \rightarrow **1715** in Scheme 60.

The thermolysis of allylaminomethylenemalonates (**1722**) at 500–550°C gave 2-cyanopent-4-enecarboxylic acid derivatives (**1723**), in which both the allyl and R^1 groups had undergone migration (Scheme 62). The formation of iminoacroleins was also not observed in these cases.

Diethyl mercapto[(2-pyridyl)amino]methylenemalonate (**1724**) was treated with methylene iodide in DMF in the presence of potassium carbonate at 50–60°C for 6 hr to give 3-(2-pyridyl)-1,3-thiazetid-2-ylidene malonate (**1725**) (89EUP312794). Thiazetidinyliidenemalonate (**1725**) was cyclized in fuming sulfuric acid at 0°C for 12 hr to give 4-oxo-1,3-thiazeto[3,2-*a*]-1,8-naphthyridine-3-carboxylic acid (**1726**) in 61% yield.

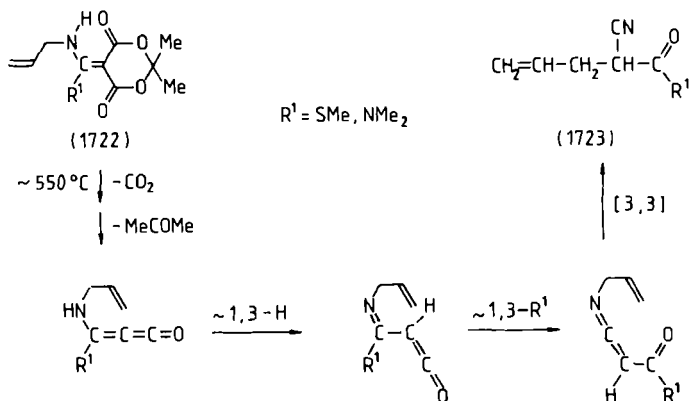


SCHEME 60

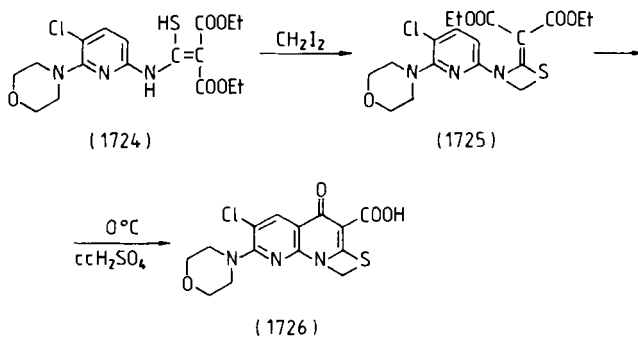


SCHEME 61

Dialkyl *N*-(benzoxazin-4-yl)methylenemalonates and their optically active forms (**1728**) were prepared in the reaction of the appropriate phenylaminomethylenemalonate (**1727**), triphenylphosphine, and diethyl azodicarboxylate in THF at -20°C (89EUP322815). The hydroxyl group of racemic and optically active phenylaminomethylenemalonates (**1727**) were tosylated with *p*-toluenesulfonyl chloride in pyridine, and the products were cyclized by heating in DMF at 80°C in the presence of potassium carbonate and a catalytic amount of 18-crown-6-ether to give **1728** (89EUP322815).

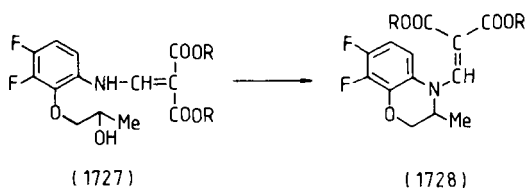


SCHEME 62

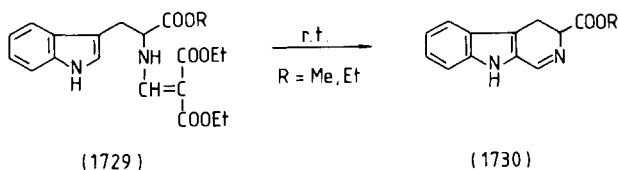


The racemic ethyl ester of **1727** ($R = \text{Et}$) was resolved by HPLC with modified silica gels [89JAP(K)261380].

The cyclization of the racemic methyl ester of **1727** ($R = \text{Me}$) and its (S) enantiomer by boron trifluoride gave 9,10-difluoro-7-oxopyrido[1,2,3-*de*]-1,4-benzoxazine-6-carboxylic acid and its optically active form, respectively [89JAP(K)228974].



When aminomethylenemalonates (**1729**) were left to stand at ambient temperature in acetonitrile in the presence of *p*-toluenesulfonic acid for 2 days, 3,4-dihydro- β -carboline derivatives (**1730**) were obtained in good yields (89AJC813).



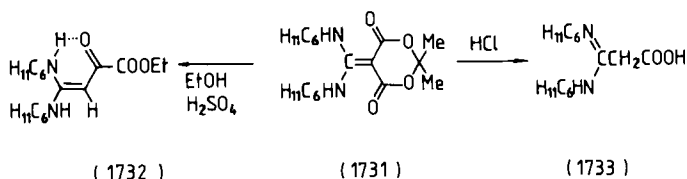
The methylenemalonate moiety was used as an *N*-protecting group at the esterification of amino acids. After the esterification of the carboxyl group with the appropriate alkyl bromide in acetone in the presence of

triethylamine at room temperature, *N*-deprotection of amino esters was readily achieved with bromine in chloroform at ambient temperature (89S544).

Benzoylation of *N*-(2,2-diethoxycarbonylvinyl)- β -D-galactopyranosylamine and - β -D-glucose analogue in pyridine with benzoyl chloride afforded mixtures of di-, tri-, and tetra-*O*-benzoyl derivatives. From 2,3,6-tri-*O*-benzoyl-*N*-(2,2-ethoxycarbonylvinyl)- β -D-galactopyranosylamine and - β -D-glucopyranosylamine the amines were liberated with bromine or chlorine in chloroform or methylene chloride (89MI4).

Ethanolysis of isopropylidene bis(cyclohexylamino)methylenemalonate (**1731**) afforded 2-oxo ester (**1732**) in boiling ethanol in the presence of sulfuric acid, and the hydrolysis of **1731** in dioxan in the presence of concentrated hydrochloric acid gave amidine (**1733**) (88ZC436).

Dimethyl *N*-(3-methyl-2(3*H*)-benzothiazol-2-ylidene)malonate was used as a secondary harmonic generating agent at the production of nonlinear optical materials [89JAP(K)205130].



C. Reaction of Dialkyl Alkoxymethylenemalonates with Amines

Ammonia: 59BCJ188; 74G715; 75JCS(P1)1517; 81JCS(P2)561,

Primary (cyclo)aliphatic amines: 41CB1111; 52JCS650; 60JA718; 62JOC306; 64JMC68; 65MI1, 65ZOR348; 67MI1; 68MI1; 69MI1; 70AP612; 72IJC686; 73GEP2322073; 74G715, 74GEP2362978; 75GEP2336723, 75JCS(P1)1517, 75JHC1245; 76IJC784, 76JCS(P1)1331; 77H1699, 77H1821, 77MI3; 78CC943, 78CPB2224; 79JAP(K)119484, 79MI1; 80EUP9609, 80GEP2947948, 80GEP3002659, 80GEP3008884, 80JAP-(K)31040; 81CPB1998, 81GEP3018132; 81JCS(P2)561; 82EUP45717, 82JAP(K)116048, 82JHC289, 82MI7; 83S946; 84MI7; 85MI3, 85TL1769; 86EUP174832, 86MI8, 86MI9, 86MIP2; 87AJC1617, 87JCS(P1)2079, 87MI4, 87T191; 89AJC813, 89GEP3825382, 89S544; 90JHC1527

Secondary aliphatic amines: 48JOC471; 62JA635; 64JMC68; 69JA6683; 75FES917; 77H1821; 78CPB2224; 80T2125; 81GEP3018132; 84USP-4444581, 84USP4444582; 86MI2; 89EUP323189, 89GEP3825382

Cyclic amines: 48JOC471; 52JCS650; 60JA4044; 61BSF2423; 62JOC306; 64JMC68; 66CB281, 66JMC774; 72JMC1203, 72MI3; 73GEP2264163; 74GEP2415763, 74USP3840522; 75USP3883522, 75USP3917609, 75ZOR420; 76MIP3, 76USP3969463, 76USP3976651, 76USP398753, 76USP3985882; 77USP4001243, 77USP4014877; 78JAP(K)-82799; 79GEP2849158, 79GEP2914218, 79GEP2914258, 79JAP(K)154797, 79JAP(K)163598; 80JAP(K)38364, 80JAP(K)145612, 80JAP(K)149284; 81BEP885605, 81FRP2463771, 81FRP2476079, 81GEP3018132, 81JAP(K)55388; 82BEP891046, 82BEP891537, 82EUP47005, 82JAP(K)203085, 82USP4348521; 83EUP79162, 83JAP(K)13585, 83JAP(K)29789, 83JAP(K)52290, 83JAP(K)90511, 83USP4380543, 83USP4404207, 83USP-4416884; 84CPB4907, 84CPB4923, 84EUP101829, 84EUP109284, 84EUP109285, 84EUP119779, 84GEP3306772, 84GEP3308908, 84JAP(K)122493, 84NEP1115, 84USP4443447, 84USP4456606; 85JAP(K)-126290, 85JAP(K)208987, 85USP452148; 86EUP174832, 86EUP184384, 86EUP203795, 86EUP206283, 86GEP3519926, 86JAP(K)204188, 86MI14, 86USP4565872; 87EUP245913, 87JMC465, 87JMC839; 88AP241, 88EUP252352, 88EUP267432, 88EUP273399, 88JAP(K)60990, 88M761; 89CPB2103, 89MI2, 89EUP310969, 89JAP(K)228974, 89JAP(K)261380, 89S544

CARBOCYCLIC AMINES

Aniline: 46JA1264, 46JCS1033; 48JCS893; 50JOC1224; 55JIC52; 63USP3079366; 74G715; 77JMC1001; 78MI2; 79MI4; 81ABC2769, 81EUP22078; 82EUP55068, 82USP4312870; 83BSF66; 86EUP174832; 89MI3, 89T889

2-Substituted anilines: 46JA1204, 46JA1264, 46JA1268, 46JA1277; 47JA371, 47JA374; 48JCS893; 49BRP627297, 49JA3236, 49JOC277; 50JCS464; 51JCE126; 52JA2637; 54JIC951; 55JIC52; 57MI2; 59JCS2401, 59MI1; 66NEP2994; 67BRP1070333; 69CJC489, 69GEP1815467; 70CR-(C)1189, 70FRP7731, 70GEP1925607; 72JMC230, 72JMC235; 73IJC1332, 73JPS834, 73MI1; 74FRP2186244, 74GEP2411523, 74GEP2421121, 74JMC137; 75JCS(P1)2409; 76MI3, 76MI4; 78JMC268; 79MI4; 80NEP1752; 82USP4343804; 84EUP116518, 84FES95; 85JMC298; 86EUP174832, 86JAP(K)106557, 86KFZ313; 87EUP245054, 87YZ123

3-Substituted anilines: 46JA1204, 46JA1264, 46JA1268; 47JA371, 47JA374; 48JCS893; 49BRP627297, 49JA3236, 49JOC277; 51JCE126; 54JIC951; 55JIC52; 63BRP942524; 66NEP2994; 67BRP1070333; 69FRP2002888, 69JMC232, 69USP3472859; 72ACH469, 72GEP2224090, 72JMC235, 72MI3; 73AJC907, 73USP3755332; 74FRP2193822, 74GEP2421121; 75BRP1396681, 75USP3907808; 76PHA145, 76SZP-578534; 77JMC1001; 78JMC268, 78YZ1291; 79MI4, 79USP4137227; 80GEP2856908, 80NEP1752; 81GEP3018132, 81JAP(K)65874; 82CPB-3517, 82EUP67772, 82IJC(B)444, 82JMC57, 82USP4343804; 83EUP70767; 84EUP116518, 84FES95, 84JHC1857; 86EUP174832, 86KFZ313; 87FES3, 87JHC1509, 87YZ123; 90JHC1177

4-Substituted anilines: 46JA1204, 46JA1264, 46JA1277; 46JCS1033; 47JA371, 47JA855, 47JA1659, 47JIC223; 48JA4063, 48JCS893; 49BRP627927, 49JOC277; 50JCS384, 50JCS607; 51JCE126; 52JPJ1112; 54JIC951; 55JIC52, 55USP2719848; 56JCS3079; 58MI1, 58MI4; 61MI2; 64IJC461; 67BRP1070333; 68SAP6075; 69FRP7375, 69FRP2002888, 69JMC357, 69USP3472859; 70GEP2033969; 72ACH469, 72GEP2146675, 72JMC235; 73AJC907, 73CI(M)542, 73MI1; 74G715, 74GEP2421121; 75BRP1396681; 76FES237, 76SZP578534, 76USP3976651, 76USP3985753; 77GEP2705446; 78JMC268, 78YZ1291; 79LA387, 79MI4; 80GEP2856908, 80NEP1752; 81JCS(P2)561; 82EUP67772, 82IJC(B)444, 82USP4343804; 83EUP70767, 83FES219; 84EUP112289, 84EUP116518, 84FRP2537139; 85USP4560692; 86EUP174832, 86EUP174833, 86KFZ313; 87FES3, 87YZ123; 90JHC1177

N-Substituted anilines: 46JA2009; 60JA718; 69BRP1147336, 69JA6683; 71JHC357; 72HCA1319; 73CI(M)542; 74GEP2246503, 74JMC137; 75JCS(P1)2409, 75JHC557; 76FES237, 76GEP2613595; 79JHC1353, 79MIP4; 79USP4146625; 80GEP3007006; 81ABC2769, 81GEP3018132; 82HCA2645; 83BSF66; 84BEP899399, 84EUP106489; 85FES237, 85GEP3433924, 85JAP(K)28964, 85JAP(K)126271, 85JAP(K)-166678, 85NKK2054, 85SAP3954, 85USP4533735; 86EUP172004, 86EUP183129, 86EUP195316, 86JAP(K)143364, 86MI13; 87JAP(K)26272, 87JIC481, 87NEP471, 87USP4636506; 89EUP304158, 89EUP332033, 89JAP(K)61461, 89JAP(K)83068, 89USP4797490, 89USP4874764

Polysubstituted anilines: 46JA1232, 46JA1264, 46JA1268; 47JA371; 48JA4063; 49BRP627297; 50JCS464; 51JCE126; 54JIC951; 58MI4; 60CB642; 63BRP942524; 64BEP640906; 65BEP659237; 66BEP670520, 66JMC934, 66NEP447, 66NEP2994; 67USP3316147; 68BRP1120870, 68BRP1122715, 68FRP1531495, 68JOC1435, 68SAP5655; 69BRP1168105, 69FRP2002888, 69GEP1908262; 70FRP7611, 70FRP7975, 70FRP1518462,

70JHC171, 70JMC870, 70USP3546225; 72ACH351, 72JMC230, 72JMC237, 72JMC937; 74GEP2246503, 74GEP2421121, 74GEP2431584, 74JHC849, 74JMC137, 74NEP8800, 74NEP11324; 75IJC1275, 75-JAP(K)49286, 75JCS(P1)2409, 75USP3907808; 76ACH91, 76HI347, 76MI2, 76MIP1, 76SZP578534; 77GEP2550519, 77JAP(K)83596, 77JAP-(K)125176, 77MI4, 77PHA223; 78GEP2747199, 78JIC193, 78JPR937, 78MI6; 79CPB1, 79EGP134225, 79GEP2840910, 79JAP(K)14978, 79JHC1353, 79MI5; 80JAP(K)33453, 80JMC1358, 80JPS933, 80NEP1752; 81EUP28698, 81FRP2463771, 81GEP3018132, 81JAP(K)65874, 81JAP-(K)128773; 82CPB3530, 82EUP62001, 82HCA2645, 82JAP(K)139014, 82JAP(K)203085, 82JHC289, 82MI5, 82SZP627755, 82USP434804; 83ACH341, 83EUP77938, 83EUP96214; 84FES910, 84FRP2537140, 84ZN(B)384; 85BEP902337, 85CPI192554, 85EUP153163, 85EUP155244, 85JAP(K)166681, 85JMC298, 85MIP1; 86EUP174832, 86EUP179239, 86EUP184384, 86FES366, 86JAP(K)37771, 86JAP(K)65882, 86JAP-(K)143363, 86JPS1185, 86MI4, 86MI7, 86MI11, 86MI13, 86MIP3; 87EUP216345, 87EUP230053, 87JAP(K)263157, 87JHC399, 87JHC1509, 87MI6, 87MIP1, 87NEP471, 87YZ123; 88EUP259804, 88EUP287951, 88JAP(K)239269, 88JHC1567, 88JPS458, 88M761, 88MI7, 88MIP1, 88USP4719302, 88USP4777252; 89CCC506, 89EUP304158, 89EUP-322815, 89EUP323189, 89JAP(K)224362, 89JAP(K)265088, 89MI105, 89USP4868305; 90JMC129, 90JMC1246

***o*-Phenylenediamines:** 46JA1320; 57MI2; 59MI1; 64JMC68; 67MI1; 68AF1214; 72GEP2220294; 78USP4123536; 81ZC286; 83JHC681; 85ZC28

***m*-Phenylenediamines:** 54JA1109; 72GEP2220294; 83JHC681; 84MI4; 85EUP134165, 85FRP2548664; 86FRP2574404

***p*-Phenylenediamines:** 49JCS1017; 86EUP174832

Aminocycloheptatrienes: 55BRP723341; 59NKZ75; 60NKZ295; 61-MI1; 68NKZ620; 83USP4381304, 83USP4382088

4-Aminoindene: 70GEP1912944; 73GEP2222818, 73GEP2222833

5-Aminoindene: 70GEP1912944

1-Aminonaphthalenes: 46JA1327; 48JCS893; 64JMC487; 71JHC357; 72HCA1319; 74JMC137; 80MI1

2-Aminonaphthalenes: 39JA2890; 46JA1327; 54JA2429; 62JOC306, 62JOC4137; 67USP3324003, 67USP3324135; 72HCA1319

5-Amino-1,2,3,4-tetrahydronaphthalenes: 69SAP5212; 70GEP1912944

6-Amino-1,2,3,4-tetrahydronaphthalenes: 69SAP5212; 70GEP1912944

- Aminonaphthohydroquinones:** 67JOC3210
1,8-Diaminonaphthalenes: 67N115
2,3-Diamino-1,4-naphthoquinone: 88LA799
1-Aminoanthracenes: 62MI2
1-Aminoanthraquinones: 59MI1; 87MI8
2-Aminoanthracenes: 62MI2
2-Aminoanthraquinones: 59MI1
1,5-Diaminoanthracenes: 62MI2
Diaminoanthraquinones: 59MI1
2-Aminophenanthrenes: 54JPJ203
2-Aminofluorenes: 51JA1844

MONOCYCLIC AMINES WITH ONE HETEROATOM

- 2-Aminofurans:** 66JHC202
2-Aminothiophenes: 75GEP2435025, 75JAP(K)77393, 75JAP(K)-77394; 76GEP2447477, 76JAP(K)48440, 76JAP(K)101127, 76JAP(K)-101128; 77JHC807; 78BEP858479, 78MI3; 80MI4; 84EUP126970
3-Aminothiophenes: 77JHC807; 78JCR(M)4701, 78JCR(S)393; 80-JCR(S)4; 82EUP46990, 82JCR(M)4701, 82JCR(S)158; 84EUP126970; 87T3295; 88EUP269295; 89JCR(S)196, 89MIP8112
2-Aminopyrroles: 75JCS(P1)1910; 80GEP3017625; 82JHC909, 82MI4; 85JCS(2)1881, 85JHC1429; 86SAP9289; 87FES787, 87JHC297; 89-JHC1029
3-Aminopyrroles: 85JHC83, 85JHC729, 85JHC817; 90JHC1201
1-Aminopyridinium salts: 73JCS(P1)2580
2-Aminopyridines: 48JA3348; 62BEP612258, 62JOC4137; 66MI1; 68JOC3015, 68USP3404153; 69CPB1832; 70BRP1208279; 71G129, 71GEP2108046, 71IJC201, 71JCS(C)2735, 71JCS(C)2985; 72AF815, 72G253, 72GEP2125310, 72JAP25349, 72JMC1203; 73BRP1322318, 73FRP2138216, 73GEP2318821, 73JAP(K)34897; 74GEP2362553; 75-JHC427, 75MIP1; 76MIP5, 76USP3960847; 77GEP2648770; 78GEP-2811483, 78KGS1671, 78MI1, 78MI5; 79BEP873195, 79GEP2906253, 79USP4169092; 80EUP9425, 80JAP(K)130980, 80MIP2; 81CPI114822, 81JAP(K)46811, 81JAP(K)131583; 82CPB2399, 82FRP2496663, 82FRP-

2500833, 82JHC909, 82MI4, 82MI5; 83JOC4132, 83KGS816; 84AJC1065, 84CPB4914, 84FRP2531084, 84GEP3308089, 84JHC673, 84KG799; 85-EUP153163, 85EUP153828, 85EUP159174, 85JAP(K)112790; 86EUP-172651, 86EUP174832, 86EUP218423, 86T3537; 87JHC215, 87JMC1622; 88EUP265230, 88MI7, 88USP4777252; 90JHC1527

3-Aminopyridines: 46JA1204, 46JA1317; 54JCS2357, 54JOC2008; 56BRP743901; 65USP3225055; 66BRP1022214, 66MI2; 69USP3429887; 70BRP1182369, 70USP3506668, 70USP3517014; 71JOC1331; 74MI2; 76NEP9159, 76SAP4716; 77GEP2607012, 77MI6; 77USP4026881; 78-BAP509, 78BRP1509695, 78JOC1331, 78USP4107315; 79CZ387, 79MIP3, 79USP4137233; 80YZ38; 81CP1103253, 81JHC941, 81MI6; 84EUP115469, 84JAP(K)93080; 85AJC459; 86EUP174832; 89EUP346207

4-Aminopyridines: 50JOC1224; 57MI3; 65USP3225055; 74GEP-2362553; 77GEP2612314, 77USP4018770, 77USP4032523; 82CPB2399, 82JHC1581, 82JMC837

1,2-Diaminopyridinium salts: 75YZ1497

2,6-Diaminopyridines: 46JA1317; 84MI4; 86EUP174832

3,4-Diaminopyridines: 59JA6297

Bis(2-aminopyridin-3-yl)disulfides: 89EUP329126

2-Aminoazepines: 73JAP(K)34897; 75MIP1; 80BEP883216; 82JHC-909, 82MI4; 84H2285; 85JCS(P2)1881

2-Aminoazocines: 82JHC909, 82MI4

MONOCYCLIC AMINES WITH TWO HETEROATOMS

3-Aminoisoxazoles: 82JAP(K)158789

5-Aminoisoxazoles: 72AP833, 72GEP2213076, 72GEP2213077; 73-GEP2237765, 73GEP2301267; 74GEP2329809; 75USP3862947, 75USP-3912737, 75USP3925388; 88JHC231

2-Aminooxazoles: 72JMC1203; 73BRP1331059

3-Aminoisothiazoles: 86EUP174832

4-Aminoisothiazoles: 86EUP174832

5-Aminoisothiazoles: 80JHC717; 82IJC(B)458; 86EUP174832

2-Aminothiazoles: 54JPJ966; 59JOC779; 62JOC306; 64IZV1481; 70IJC499; 72JMC1203; 73BRP1331059, 73GEP2241241; 74CPB243; 76GEP2264979; 77GEP2648770; 79JHC1021; 81FRP2470132; 83JAP-(K)198405, 83JAP(K)198474, 83JAP(K)198485; 87IJC(B)654

4-Aminothiazoles: 84JHC1361

5-Aminothiazoles: 71JAP43792; 84JHC401

3(5)-Aminopyrazoles: 50JOC779; 62CPB620; 68BRP1115254; 70CB-3252, 70GEP2028869; 71GEP2028828, 71GEP2123318, 71GEP2125631, 71IJC201, 71SAP887; 72GEP2138528, 72GEP2138529, 72GEP2159600, 72GEP2159601, 72JHC235, 72USP3669950; 73GEP2237765, 73GEP-2257547, 73GEP2258687, 73GEP2261444, 73JAP(K)81892; 74AP177, 74BRP1351775, 74FRP2200003, 74GEP2333603, 74GEP2346466, 74GEP-2356684, 74USP3850546; 75GEP2446495, 75JMC312, 75USP3925388, 75USP3928362, 75USP3928368; 76GEP2617157, 76USP3966746, 76USP-3979399, 76USP3983128; 77CP1003419, 77GEP2646670, 77GEP2648770, 77IJC(B)349, 77USP4020072, 77USP4021556, 77USP4038283; 78IJC(B)-161; 81FES441; 82JMC235, 82JPR557; 83EUP70376, 83EUP94175, 83EUP96995, 83GEP3309432; 84USP4448973; 85JHC601; 86EUP174832, 86USP4563525; 87MI2; 88CJC420; 89EUP304001, 89JMC2561

4-Aminopyrazoles: 76JCS(P1)507; 77JAP(K)77086

3,4-Diaminopyrazoles: 83JCS(P1)11

2-Aminoimidazoles: 51BSB69; 59JOC779; 82IJC(B)1030

3-Aminopyridazines: 68TL33; 71JOC2457; 72HC351; 78GEP2814777; 80USP4231928; 85H1; 86MI6; 88JHC1535

2-Aminopyrimidines: 58MI2; 59MI3; 60JA718; 62JOC306, 68AF1214; 72JMC1203; 79GEP2758115

4-Aminopyrimidines: 67USP3320257; 68AF1214, 68JAP6227; 70-CPB1385; 71CPB1426, 71CPB1482; 72JOC3980, 72USP3673184; 75-JAP(K)58082; 76GEP2544369, 76USP3992380; 80CPB2148; 84JHC247; 85JHC1469, 85JHC1735; 87JAP(K)142177, 87MIP6; 88JAP(K)183582; 89JHC1089; 90JHC1963

5-Aminopyrimidines: 67JCS(C)1745, 67USP3320257; 68AF1214

2-Aminopyrazines: 68JMC1045; 70T3069; 71IJC201, 72CB3118; 73JAP(K)23798; 74CPB1864, 74JAP(K)56996; 75JAP(K)53394, 75YZ1092; 89EUP329126

MONOCYCLIC AMINES WITH THREE HETEROATOMS

3-Amino-1,2,4-oxadiazoles: 63JCS6028

2-Amino-1,3,4-oxadiazoles: 67EGP56240; 70AP501; 86IJC(B)654; 88IJC(B)293

- 3-Amino-1,2,5-oxadiazoles:** 73JPR791
- 3,4-Diamino-1,2,5-oxadiazoles:** 79KGS319
- 3-Amino-1,2,4-thiadiazoles:** 77JHC621
- 5-Amino-1,2,4-thiadiazoles:** 59JOC779
- 2-Amino-1,3,4-thiadiazoles:** 59JOC779; 64IZV1481; 73ABC1197; 84GEP3346223; 85EUP150507; 86FES737, 86IJC(B)654; 87EUP238997
- 3(5)-Amino-1,2,3-triazoles:** 71JCS(C)2156
- 3-Amino-1,2,4-triazoles:** 48USP2449226; 49USP2476549; 62JCS2222; 67JCS(C)503; 74GEP2327133; 77GEP2648770; 80JCS(P1)1347; 82JMC420, 85EUP150507; 86GEP3602367; 87GEP3522463; 89IJC(B)242

BICYCLIC AMINES WITH ONE HETEROATOM

- 2-Aminocyclopenta[*b*]thiophene:** 76GEP2447477
- 2-Aminocyclopenta[*d*]thiazole:** 81FRP2470132
- 2-Aminobenzo[*b*]furan:** 78BEP858479, 78MI3
- 4-Aminobenzo[*b*]furan:** 70JMC1110
- 5-Aminobenzo[*b*]furan:** 69GEP1908542; 70GEP2021100, 70JMC1110; 71BRP1240446, 71GEP2030899; 72LA55
- 6-Aminobenzo[*b*]furan:** 70GEP2021100, 70JMC1110; 71BRP1240446; 75GEP2416519; 77MI4
- 7-Aminobenzo[*b*]furan:** 70GEP2021100, 70JMC1110; 71BRP1240446, 71FRP2043498
- 4-Aminobenzo[*c*]furan:** 69FRP2002888
- 5-Aminobenzo[*c*]furan:** 71GEP2030899
- 2-Aminobenzo[*b*]thiophen:** 75GEP2435025
- 3-Aminobenzo[*b*]thiophen:** 76JAP(K)136698
- 5-Aminobenzo[*b*]thiophen:** 72LA55
- 6-Aminobenzo[*b*]thiophen:** 88AP241, 88MI5
- 3-Aminoindole:** 76JAP(K)136698
- 5-Aminoindole:** 72LA55; 77MI4; 79KGS1084; 84MI2
- 6-Aminoindole:** 79KGS1084

- 7-Aminoindole:** 75JCS(P1)2409
- 2-Aminoisoindole:** 86EUP174832
- 4-Aminoisoindole:** 87MI1
- 5-Aminoisoindole:** 87MI1
- 3-Aminocyclopenta[*c*]pyridine:** 83KGS1279; 84KFZ931
- 2-Aminocyclohepta[*b*]pyrroles:** 87BCJ1053
- 3-Aminocoumarins:** 77JHC1009; 80USP4210758; 81JHC697
- 4-Aminocoumarins:** 81JHC697
- 6-Aminocoumarins:** 67USP3313818
- 2-Aminochromones:** 78USP4117134
- 3-Aminochromones:** 78USP4066655; 81JHC697
- 6-Aminochromones:** 70GEP1936393; 72BRP1283900
- 7-Aminochromones:** 70GEP1936393; 82BRP1283900; 80GEP2943658
- 3-Aminothiochromones:** 85JHC89
- 2-Aminoquinolines:** 59MI3; 71IJC201; 72JMC1203; 74MIP1; 75-GEP2513930; 77GEP2628751, 77GEP2630469, 77USP4031217; 78GEP-2801248; 79MIP1, 79USP4175193; 85EUP174832
- 3-Aminoquinolines:** 50JOC1224; 67USP3300499; 72JAP35919; 88-GEP3628356
- 4-Aminoquinolines:** 50JOC1224; 58JCS828, 70JMC230; 86EUP174832
- 5-Aminoquinolines:** 59MI3; 80JAP(K)69582; 86EUP174832; 88USP-4719302
- 6-Aminoquinolines:** 49JCS1017; 78JAP(K)28196
- 7-Aminoquinolines:** 86EUP174832; 88USP4719302
- 8-Aminoquinolines:** 46JA1320; 59MI3; 62JOC3878; 72JMC1203
- 1-Aminoisoquinolines:** 78USP4127720; 84JAP(K)172472; 85EUP-143001
- 3-Aminoisoquinolines:** 83KGS1279; 84KFZ931; 88MI9
- 5-Aminoisoquinolines:** 83HCA620
- 7-Aminoisoquinolines:** 81EUP27904

BICYCLIC AMINES WITH TWO HETEROATOMS

5-Aminofuro[2,3-*b*]pyridines: 77MI6

2-Aminofuro[3,2-*b*]pyridines: 84G211

5-Aminofuro[3,2-*b*]pyridines: 84CPB4914

4-Aminobenzo(*d*)-1,3-benzodioxoles: 79JMC1354

5-Aminobenzo(*d*)dioxolanes: 66FRP4148; 68JMC160; 69FRP2002888; 71GEP2033971, 71JHC357; 72JHS(P1)173; 76ACH91, 76GEP2534869, 76JAP(K)18440, 76JAP(K)86497, 76MIP4; 78USP4086236; 79MI3; 83ACH241, 88MI7

5-Amino-1,3-benzodithioles: 86MI339

3-Amino-1,2-benzisoxazoles: 82JAP(K)158789

2-Aminobenzoxazoles: 68SAP7052; 72JMC1203; 73CPB2019; 79-JOC1811

6-Aminobenzoxazoles: 74JAP(K)72297

3-Amino-1,2-benzisothiazole-1,1-dioxides: 70IJC499

5-Amino-2,1-benzisothiazoles: JAP(K)61500; 74JAP(K)18893; 75JAP-(K)84596

5-Amino-2,1-benzisothiazole 1,1-dioxides: 74JAP(K)75596

2-Aminobenzothiazoles: 68SAP7052, 68SAP7053, 68YZ1003; 71-JCS(C)2094; 72JMC1203; 73CPB2019, 73GEP2241241, 73JCS(P1)1588, 73JHC769; 76GEP2264979; 79GEP2810863, 79JOC1811, 79SAP1053; 81FRP2470132

4-Aminobenzothiazoles: 77JAP(K)83596, 77JAP(K)125196; 79CPB1

5-Aminobenzothiazoles: 74JAP(K)88882; 77JAP(K)125196; 79CPB1

6-Aminobenzothiazoles: 71GEP2056224, 71GEP2119396; 73JAP(K)-23800; 75GEP2449544, 75JAP(K)46698, 76JAP(K)52094; 76CPB130, 76CPB1050; 77JAP(K)83596, 77JAP(K)125196; 79CPB1

7-Aminobenzothiazoles: 77JAP(K)83596, 77JAP(K)125196; 79CPB1

3-Aminoindazoles: 76T493; 78GEP2822124; 80MI3

4-Aminoindazoles: 78GEP2822124; 80MI3

5-Aminoindazoles: 78GEP2822124, 78YZ1063; 79JAP(K)32496; 80MI3

6-Aminoindazoles: 77JHC1175, 78GEP2822124, 78JAP(K)119895, 78-JAP(K)124299; 79USP4160093; 80MI3; 83JHC1351; 84MI2

7-Aminoindazoles: 78GEP2822124; 80MI3

2-Aminobenzimidazoles: 51BSB69; 72JMC1203; 73CPB2019, 73-JHC71; 78USP4072679, 78USP4109087, 78USP4109091; 79JOC1811

5(6)-Aminobenzimidazoles: 75JHC1319; 78JAP(K)50197; 79JAP(K)-144398; 80JAP(K)28920; 82MI1; 86EUP187705; 88MI13; 89CCC-713; 89KFZ692

2-Aminopyrazolo[1,5-*a*]pyridines: 77JAP(K)17497, 77JAP(K)36695

7-Aminopyrazolo[1,5-*a*]pyrimidines: 77GEP2650780

7-Amino-7*H*-pyrrolo[2,3-*d*]pyrimidines: 75JHC1291

3-Aminoimidazo[1,2-*a*]pyridines: 81JHC1565

2-Aminocyclohepta[*d*]thiazoles: 81FRP2470132

5-Amino-1,3-benzodioxanes: 72MI5

6-Amino-1,3-benzodioxanes: 70GEP1936393; 72BRP1283900, 72CR-(D)1583, 72GEP2139212, 72MI4, 72MI5

7-Amino-1,3-benzodioxanes: 72MI4, 72MI5

8-Amino-1,3-benzodioxanes: 72MI5

6-Amino-1,4-benzodioxanes: 69FRP2002888, 69GEP1814187; 70GEP-1936393; 72BRP1283900; 73GEP2303496; 75KGS1663; 76JMC982; 81-JOC3846

3-Amino-2*H*-1,4-benzoxazines: 81USP4254118

6-Amino-4*H*-1,4-benzoxazines: 88IJC(B)649

7-Amino-4*H*-1,4-benzoxazines: 78JAP(K)28196

3-Amino-2*H*-1,4-benzothiazines: 81USP4254118

5-Amino-2*H*-1,4-benzothiazines: 84MI5

6-Amino-2*H*-1,4-benzothiazines: 84MI5

7-Amino-2*H*-1,4-benzothiazines: 84MI5

8-Amino-2*H*-1,4-benzothiazines: 84MI5

2-Amino-1,5-naphthyridines: 78MI7

4-Amino-1,5-naphthyridines: 59JA6297

- 2-Amino-1,6-naphthyridines:** 74JHC151
2-Amino-1,8-naphthyridines: 71G129, 71JCS(C)2985; 80FES1052
3-Amino-1,8-naphthyridines: 78YZ1279
8-Aminocinnolines: 51JOC1414
2-Aminoquinazolines: 89JHC161
4-Aminoquinazolines: 81EUP30156; 86JAP(K)50983
6-Aminoquinazolines: 78JAP(K)147095; 79GEP2833018
1-Aminophthalazine: 74CR(C)209
7-Amino-1,4-benzodioxepines: 69GEP1814187
2-Amino-3H-1,4-benzodiazepines: 74GEP2400449

BICYCLIC AMINES WITH THREE OR MORE HETEROATOMS

- 4-Amino-2,1,3-benzothiadiazoles:** 76KGS61; 84MI2
5-Amino-2,1,3-benzothiadiazoles: 74JAP(K)15498
5(6)-Amino-1H-benzotriazoles: 88MI13; 89CCC713
2-Aminopyrido[3,2-*d*]thiazoles: 73JHC769
3-Amino-1H-pyrazolo[3,4-*b*]pyridines: 77IJC(B)349; 87MI5
3-Amino-1H-pyrazolo[3,4-*d*]pyrimidines: 89JCR(S)333
5-Amino-1H-pyrazolo[3,4-*b*]pyridines: 81MI1
5-Amino-1H-pyrazolo[4,3-*b*]pyridines: 81MI1
5-Amino-3H-imidazo[4,5-*b*]pyridines: 86EUP174832
3-Amino-4H-1,2,4-benzothiadiazine 1,1-dioxides: 89JHC473
1-Aminopyrido[4,3-*d*]pyrimidines: 84KGS532
6-Aminopurines (adenines): 86EUP174832
4-Aminonaphthalimides: 86IJC(B)652

TRICYCLIC AMINE WITH ONE HETEROATOM

- 8-Amino-1,2,3,4-tetrahydrodibenzofurans:** 69GEP1908542;
70GEP2021100; 71BRP1240446
1-Aminocarbazoles: 52JOC1501
3-Aminocarbazoles: 52JOC1501; 87CPB425, 87FES641; 88MI6

3-Aminoacridines: 77JAP(K)3099, 77USP4060527

6-Aminomorphanthridines: 80JHC341

TRICYCLIC AMINES WITH TWO HETEROATOMS

2-Aminonaphtho[1,2-*d*]thiazoles: 68SAP7052, 68SAP7053; 70FRP-7834; 72JMC1203

2-Aminonaphtho[2,1-*d*]thiazoles: 68SAP7052, 68SAP7053; 85AP84

3-Amino-9*H*-pyrido[3,4-*b*]indoles: 87MIP4, 87MIP5; 88IJC(B)484

2-Aminobenzo[4,5]cyclohepta[*d*]thiazoles: 69NKZ569

2-Aminophenothiazines: 79JAP(K)30198

4-Aminobenzo[*h*]quinazolines: 86H1119

2-Aminoperimidines: 89AP303

11-Amino-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepines: 85CP1197242, 85JHC305

11-Aminodibenzo(*b,f*)[1,4]thiazepines: 80JHC341

11-Amino-5*H*-dibenzo(*b,e*)[1,4]diazepines: 80JHC341

TRICYCLIC AMINES WITH THREE OR MORE HETEROATOMS

6-Aminoimidazo[2,1-*b*]benzothiazoles: 81EUP21806

7-Aminoimidazo[2,1-*b*]benzothiazoles: 81EUP21806

8-Aminoimidazo[2,1-*b*]benzothiazoles: 81EUP21806

8-Aminothiazolo[3,4,5-*de*]quinoxalines: 78JAP(K)28196

7-Amino-1,2,4-triazolo[4,3-*a*]quinolines: 86EUP174833

2-Aminoanthryridines: 74FES366

2-Amino-1,3-dioxolo[*f*]benzothiazoles: 73JHC769

3-Amino-1,2,4-triazolo[3,4-*b*]benzoxazoles: 89H925

3-Amino-1*H*-pyrazolo[3,4-*d*]thieno[2,3-*b*]pyridines: 83M1079

TETRACYCLIC AMINES

2-Aminopyrido[3,2,1-*d,e*]dibenzo(*b,f*)[1,4]oxazepines: 74IJC252

D. Ring Systems Obtained by Ring Closure of Dialkyl Aminomethylenemalonates

4-Hydroxypyridine-3-carboxylates: 75JHC1245; 77JHC477; 78JAP(K)-63382; 88EUP270494, 88GEP3808444

4-Hydroxyquinoline-3-carboxylates: 39JA2890; 46JA1204, 46JA1232, 46JA1264, 46JA1268, 46JA1277, 46JCS1033; 47JA371, 47JA374, 47JA855, 47JA1659; 48JA4063, 48JCS893; 49BRP627297, 49JA3236, 49JOC277; 50JCS384, 50JCS464, 50JCS607, 50USP2494801; 51JCE126; 52JA2637, 52JPJ1112; 54JIC951; 55USP2719848; 56JCS3079; 57MI2; 58MI1, 58MI4; 59MI1; 60CB642; 62MI2; 63BRP942524, 63MI2; 64BEP640906, 64IJC461; 65BEP659237; 66BEP670520, 66FRP4148, 66JMC934, 66NEP2994; 67-USP3316147; 68BRP1120870, 68BRP1122715, 68FRP1531495, 68SAP-5655, 68SAP6075; 69BRP1147336, 69BRP1168105, 69FRP7375, 69FRP-2002888, 69GEP1815467, 69GEP1908262, 69JMC232, 69USP3472859; 70CR(C)1189, 70FRP7611, 70FRP7731, 70FRP7975, 70FRP1581462, 70GEP1925607, 70GEP2033969, 70JHC171, 70JMC870, 70MIP3; 71JHC-357; 72ACH351, 72ACH469, 72GEP2146675, 72GEP2224090, 72HCA-1319, 72JMC230, 72JMC235, 72JMC237, 72JMC937, 72MI3; 73AJC907, 73CI(M)542, 73MI1, 73USP3755332; 74BEP819195, 74FRP2186244, 74-FRP2193822, 74GEP2246503, 74GEP2411523, 74GEP2421121, 74GEP-2431584, 74JAP(K)32933, 74JHC849, 74JMC137, 74NEP8800, 74NEP-11324; 75BRP1396681, 75GEP2343462, 75JAP(K)49286, 75JCS(PI)2409, 75JHC557, 75JHC1245, 75USP3907808; 76FES237, 76H1347, 76MI3, 76MI4, 76MI5, 76MIP1, 76PHA145, 76SZP578534, 76USP3976651, 76-USP3985753; 77GEP2705446, 77JAP(K)83596, 77JAP(K)125196, 77JMC-1001, 77MI2, 77MI4, 77PHA223; 78JIC193, 78JMC268, 78JPR937, 78MI4, 78MI6, 78USP4123536, 78YZ1291; 79CPB1, 79EGP134225, 79GEP-2840910, 79JAP(K)14978, 79JAP(K)119484, 79JHC1353, 79LA387, 79MI4, 79MI5, 79USP4137227; 80G155, 80GEP2856908, 80GEP2947948, 80GEP-3007006, 80GEP3008884, 80JAP(K)38364, 80JMC1358, 80NEP1752; 81EUP22078, 81EUP28698, 81FRP2463771, 81JAP(K)65874; 82CPB3517, 82CPB3530, 82EUP55068, 82EUP62001, 82EUP67772, 82HCA2645, 82IJC(B)444, 82JAP(K)116048, 82JAP(K)139014, 82JAP(K)203085, 82-JHC289, 82JMC57, 82MI5, 82USP4312870, 82USP4343804; 83ACH241, 83EUP70767, 83EUP96214, 83FES219, 83JAP(K)174367; 84BEP899399; 85EUP134165, 85EUP153163, 85EUP155244, 85FES237, 85FRP2548664, 85GEP3433924, 85JAP(K)28964, 85JAP(K)126271, 85JAP(K)166678, 85-JAP(K)166681, 85JMC298, 85MIP1, 85NKK2054, 85SAP3954, 85USP-4533735, 85USP4560692; 86EUP168350, 86EUP172004, 86EUP179239,

86EUP183129, 86EUP184384, 86EUP195316, 86FES366, 86FRP2574-404, 86JAP(K)37771, 86JAP(K)65882, 86JAP(K)106557, 86JAP(K)-143363, 86JAP(K)143364, 86JPS1185, 86KFZ313, 86M1339, 86MI4, 86MI13, 86MIP3; 87EUP216345, 87EUP230053, 87EUP245054, 87FES3, 87JAP(K)26272, 87JAP(K)263157, 87JHC399, 87MI6, 87MI7, 87MIP2, 87USP4636506, 87USP4647566, 87YZ123; 88EUP259804, 88EUP293-071, 88JAP(K)239269, 88JHC1567, 88JPS458, 88M761, 88MI3, 88-MIP1, 88USP4777252, 88ZN(B)769; 89CCC506, 89EUP304158, 89JAP-(K)224362, 89JAP(K)265088, 89T889, 89USP4868305; 90JHC1177, 90JMC1246

4-Hydroxycyclopenta(*b*)pyridine-3-carboxylates: 75JHC1245

4-Hydroxycyclohepta(*b*)pyridine-3-carboxylates: 55BRP723341; 59-NKZ75; 60NKZ295; 68NKZ620; 75JHC1245; 83USP4381304, 83USP-4382088

4-Hydroxycycloocta(*b*)pyridine-3-carboxylates: 88EUP270494

4-Hydroxycyclodeca(*b*)pyridine-3-carboxylates: 88EUP270494

4-Hydroxycyclododeca(*b*)pyridine-3-carboxylates: 88EUP270494

2-Oxypyrrolo[1,2-*a*]pyrimidine-3-carboxylates: 80GEP3017625; 82-JHC909, 82MI4

4-Oxopyrrolo[1,2-*a*]pyrimidine-3-carboxylates: 80GEP3017625; 82-JHC909, 82MI4; 85JCS(P2)1881; 86SAP9289; 87FES787, 87JHC297

4-Hydroxypyrrolo[2,3-*b*]pyridine-3-carboxylates: 75JCS(P1)1910; 85-JHC1429; 89JHC1029

7-Hydroxypyrrolo[3,2-*b*]pyridine-6-carboxylates: 85JHC83; 89JHC-1029; 90JHC1201

4-Hydroxypyrrolo[3,4-*b*]pyridine-3-carboxylates: 85JHC729

4-Hydroxyfuro[2,3-*b*]pyridine-5-carboxylates: 66JHC202

4-Hydroxythieno[2,3-*b*]pyridine-5-carboxylates: 75GEP2435025, 75-JAP(K)77393, 75JAP(K)77394; 76GEP2447477, 76JAP(K)48440, 76JAP-(K)101128; 77JHC807; 78BEP858479, 78MI3; 80MI4; 84EUP126970; 85-EUP161235; 87MI3

7-Hydroxythieno[3,2-*b*]pyridine-6-carboxylates: 77JHC807; 78JCR-(M)4701, 78JCR(S)393; 82EUP46990, 82JAP(K)116077, 82JCR(M)4701, 82JCR(S)158; 84EUP126970; 87T3295, 87USP4647566; 88EUP269295

- 4-Hydroxythieno[3,4-*b*]pyridine-3-carboxylates:** 80JCR(S)4
- 4-Oxoisoxazolo[2,3-*a*]pyridine-3-carboxylates:** 82JAP(K)158789
- 4-Hydroxyisoxazolo[5,4-*b*]pyridine-5-carboxylates:** 72AP833, 72GEP-2213076; 73GEP2237765, 73GEP2301267; 74GEP2329809; 75USP3862947, 75USP3912737, 75USP3925388; 88JHC231
- 4-Hydroxyisothiazolo[5,4-*b*]pyridine-5-carboxylates:** 80JHC717; 82-IJC(B)458
- 5-Oxooxazolo[3,2-*a*]pyrimidine-6-carboxylates:** 73BRP1331059
- 5-Oxothiazolo[3,2-*a*]pyrimidine-6-carboxylates:** 54JPJ966; 59JOC779; 64IZV1481; 72JMC1203; 73BRP1331059, 73GEP2241241; 74CPB243; 76GEP2264979; 77GEP2648770; 81FRP2470132; 86IJC(B)654
- 4-Hydroxythiazolo[5,4-*b*]pyrimidine-5-carboxylates:** 71JAP43792; 84-JHC401
- 7-Hydroxypyrazolo[1,5-*a*]pyrimidine-6-carboxylates:** 59JOC779; 62-CPB620; 70CB3252; 71IJC201; 73GEP2257547; 74API77; 75JMC312; 77-GEP2648770, 77IJC(B)349, 77USP4021556; 81FES441; 82JMC235; 83-GEP3309432, 83JCS(P1)11; 85JHC601; 89EUP304001
- 4-Hydroxypyrazolo[3,4-*b*]pyridine-5-carboxylates:** 68BRP1115254; 71-GEP2028828, 71GEP2123318, 71GEP2125631, 71SAP887; 72GEP2138528, 72GEP2138529, 72GEP2159600, 72GEP2159601, 72JHC235, 72USP366-9950; 73GEP2237765, 73GEP2258687, 73GEP2261444, 73GEP2301268, 73JAP(K)81892; 74API77, 74BRP1351775, 74GEP2346466, 74GEP-2356684, 74FRP2200003, 74USP3840546; 75GEP2446495, 75USP3925388, 75USP3928362, 75USP3928368; 76GEP2617157, 76USP3966746, 76USP-3979399, 76USP3983128; 77GEP2646670, 77CP1003419, 77USP4020072, 77USP4038281, 77USP4038283; 78IJC(B)161; 82JPR557; 83EUP94175, 83EUP96995; 86USP4563525; 87MI2; 89JMC2561
- 7-Hydroxypyrazolo[4,3-*b*]pyridine-6-carboxylates:** 76JCS(P1)507; 77-JAP(K)77086
- 5-Hydroxyimidazo[1,2-*a*]pyrimidine-6-carboxylates:** 51BSB69; 59JO-C779; 82IJC(B)1030
- 5-Hydroxy-1,2,4-oxadiazolo[4,3-*a*]pyrimidine-6-carboxylates:** 63JCS-6028
- 5-Oxo-1,3,4-oxadiazolo[3,2-*a*]pyrimidine-6-carboxylates:** 67EGP56-240; 70AP501; 86IJC(B)654; 88IJC(B)293

5-Oxo[1,3,4]thiadiazolo[3,2-*a*]pyrimidine-6-carboxylates: 59JOC779; 64IZV1481; 73ABC1197; 84GEP3346223; 85EUP150507; 86FES737, 86IJC(B)654; 87EUP238997

5-Oxo[1,2,4]thiadiazolo[4,5-*a*]pyrimidine-5-carboxylates: 59JOC779

5-Hydroxy[1,2,4]triazolo[1,5-*a*]pyrimidine-6-carboxylates: 67JCS(C)-503

7-Hydroxy-1,2,4-triazolo[1,5-*a*]pyrimidine-6-carboxylates: 67JCS(C)-503; 74GEP2327133; 77GEP2648770; 80JCS(P1)1347; 82JMC420; 85-EUP150507; 87GEP3522463; 88IJC(B)825

7-Hydroxy[1,2,3]triazolo[1,5-*a*]pyrimidine-6-carboxylates: 71JCS(C)-2156

4-Hydroxythiopyrano[4,3-*b*]pyridine-3-carboxylates: 86EUP168350; 87USP4647566

4-Hydroxypyran[4,3-*b*]pyridine-3-carboxylates: 86EUP168350; 87-USP4647566

4-Hydroxy-1,5-naphthyridine-3-carboxylates: 46JA1204, 46JA1317; 54-JCS2357; 65USP3225055; 66M12; 71JOC1331; 77GEP2607012, 77M16, 77USP4026881; 78BRP1509695, 78JOC1331; 79MIP3; 80YZ38; 81M16; 84JAP(K)93080; 85AJC459; 89EUP346207

4-Hydroxy-1,6-naphthyridine-3-carboxylates: 50JOC1224; 57M13; 65-USP3225055; 74GEP2362553, 74RC321; 76NEP9159, 76SAP4716; 82-CPB2399; 86EUP168350; 87USP4647566

4-Hydroxy-1,7-naphthyridine-3-carboxylates: 54JOC2008; 56BRP743-901; 66BRP1022214; 69USP3429887; 70BRP1182369, 70USP3506668, 70-USP3517014; 81JHC941; 84EUP115469

2-Oxopyrido[1,2-*a*]pyrimidine-3-carboxylates: 82JHC909, 82M14

4-Oxopyrido[1,2-*a*]pyrimidine-3-carboxylates: 48JA3348; 52JA5491; 68JOC3015; 71IJC201, 71JCS(C)2735; 72AF815, 72MIP1, 72MIP2; 73-GEP2318821, 73M12; 74MIP2; 75JHC427, 75MIP2; 76USP3960847; 77GEP2648770, 77JCS(P1)789, 77MIP1; 79BEP873195; 80MIP2; 82JHC-909, 82M14; 83KGS816; 84KGS799, 84S152; 85JHC481; 86EUP218-423; 88USP477252; 89TL1529

Bis(3-ethoxycarbonyl-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-9-yl)disulfides: 89EUP329126

4-Hydroxy-1,8-naphthyridine-3-carboxylates: 46JA1317; 48JA3348; 62BEP612258; 66M11; 68USP3404153; 69CPB1832; 70BRP1208279; 71-

G129, 71GEP2108046; 72G253, 72GEP2125310, 72JMC1203; 73BRP132-2318, 73FRP2138216, 73MI2, 73MIP3; 74BEP819195, 74GEP2362553; 75GEP2343462; 76MIP5, 76NEP3192; 77JAP(K)139094, 77JCS(P1)789; 78GEP2811483, 78KGS1671; 79BEP873195, 79GEP2855279; 79USP-4169092; 80EUP9425, 80JAP(K)130980; 81JAP(K)46811, 81JAP(K)-131583; 82CPB2399, 82FRP2496663, 82FRP2500833, 82MI5; 84AJC1065, 84CPB4914, 84FRP2531084, 84JAP(K)80683, 84JHC673; 85EUP153163, 85EUP153828, 85EUP159174, 85JAP(K)112790, 85JHC481; 86EUP-172651; 87JHC215, 87JMC1622

4-Oxopyrimido[1,2-*b*]pyridazine-3-carboxylates: 68TL33; 71JOC2457; 78GEP2814777; 80USP4231928; 85H1; 86MI6; 88JHC1535

5-Hydroxypyrido[2,3-*c*]pyridazine-6-carboxylates: 72JHC351

4-Oxopyrimido[1,6-*a*]pyrimidine-3-carboxylates: 72JOC3980; 80CPB-2148; 82JHC1581; 90JHC1963

5-Hydroxypyrido[2,3-*d*]pyrimidine-6-carboxylates: 67USP3320257; 70CPB1385; 71CPB1426, 71CPB1482; 72JOC3980, 72USP3673184; 73-JAP(K)8800, 73JAP(K)91093; 74GEP2341146; 76GEP2544369, 76USP-3992380; 77GEP2729661, 77JAP(K)139094; 79GEP2856527; 82JHC1581; 88JAP(K)183582; 89JHC1089

8-Hydroxypyrido[3,2-*b*]pyrimidine-7-carboxylates: 67JCS(C)1745, 67-USP3320257

4-Oxopyrazino[1,2-*a*]pyrimidine-3-carboxylates: 68JMC1045; 74CPB-1864; 75YZ1092; 89EUP32126

8-Hydroxypyrido[2,3-*b*]pyrazine-7-carboxylates: 72CB3118; 73JAP-(K)23798; 74CPB1864, 74JAP(K)56996; 75JAP(K)53394, 75YZ1092

4-Hydroxycyclopenta[4,5]thieno[2,3-*b*]pyridine-3-carboxylates: 76-GEP2447477

4-Oxocyclopenta[*g*]thiazolo[3,2-*a*]pyrimidine-3-carboxylates: 81-FRP2470132

4-Hydroxycyclopentano[*g*]quinoline-3-carboxylates: 69SAP5212

4-Hydroxycyclopentano[*h*]quinoline-3-carboxylates: 69SAP5212; 73-GEP2222818, 73GEP2222833

6-Oxopyrrolo[3,2,1-*ij*]quinoline-5-carboxylates: 72MI3; 75USP391-7609; 78JAP(K)82799; 79GEP2914218, 79GEP2914258; 80JAP(K)145612, 80JAP(K)149284; 82BEP891046, 82BEP891537; 83JAP(K)13585, 83-JAP(K)90511

- 9-Hydroxyfuro[2,3-*f*]quinoline-3-carboxylates:** 70GEP2021100; 71-BRP1240446
- 9-Hydroxyfuro[3,2-*f*]quinoline-3-carboxylates:** 70GEP2021100, 70-JMC1110; 71BRP1240446, 71GEP2030899; 72LA55; 74GEP2335760
- 9-Hydroxyfuro[3,4-*f*]quinoline-8-carboxylates:** 71GEP2030899
- 8-Hydroxyfuro[2,3-*g*]quinoline-7-carboxylates:** 69GEP1908542; 70-GEP2021100, 70JMC1110; 71BRP1240446, 71GEP2030899; 72LA55; 74-GEP2335760
- 5-Hydroxyfuro[3,2-*g*]quinoline-6-carboxylates:** 70JMC1110; 75GEP-2416519
- 4-Hydroxyfuro[3,4-*g*]quinoline-3-carboxylates:** 71GEP2030899
- 4-Hydroxyfuro[2,3-*h*]quinoline-3-carboxylates:** 70JMC1110
- 6-Hydroxyfuro[3,2-*h*]quinoline-7-carboxylates:** 70GEP202110, 70-JMC1110; 71BRP1240446
- 4-Hydroxy-[1]benzothieno[2,3-*b*]pyridine-3-carboxylates:** 75GEP24-35025; 78BEP858479, 78MI3
- 4-Hydroxy-[1]benzothieno[3,2-*b*]pyridine-3-carboxylates:** 76JAP(K)-136698
- 9-Hydroxythieno[2,3-*f*]quinoline-8-carboxylates:** 88AP241, 88MI5
- 9-Hydroxythieno[3,2-*f*]quinoline-8-carboxylates:** 72LA55
- 5-Hydroxythieno[3,2-*g*]quinoline-6-carboxylates:** 88AP241
- 5-Oxothiazolo[3,2-*a*]quinoline-4-carboxylates:** 82EUP58392
- 9-Hydroxypyrrolo[2,3-*f*]quinoline-8-carboxylates:** 79KGS1084
- 9-Hydroxypyrrolo[3,2-*f*]quinoline-8-carboxylates:** 72LA55; 79KGS-1084, 84MI2
- 8-Hydroxypyrrolo[2,3-*g*]quinoline-7-carboxylates:** 77MI4
- 4-Hydroxypyrrolo[3,4-*g*]quinoline-3-carboxylates:** 87MI1
- 6-Hydroxypyrrolo[3,2-*h*]quinoline-7-carboxylates:** 75JCS(P1)2409
- 4-Hydroxypyrrolo[3,4-*h*]quinoline-3-carboxylates:** 87MI1
- 4-Hydroxypyrido[3,2-*b*]indole-3-carboxylates:** 76JAP(K)136698; 85-ZOR432

- 4-Hydroxypyrido[2,3-*a*]indolizine-3-carboxylates:** 85JHC817
- 4-Oxocyclopenta[4,5]pyrido[1,2-*a*]pyrimidine-3-carboxylates:** 83KG-S1279; 84KFZ931
- 8-Hydroxy-1,3-dioxolo[4,5-*g*]quinoline-7-carboxylates:** 66FRP4148; 68JMC160; 69FRP2002888; 71GEP2033971, 71JHC357; 72JCS(P1)173; 73GEP2227743, 73JAP6479; 74BEP819195, 74MI2; 76GEP2534869, 76-JAP(K)18440, 76JAP(K)86497, 76MIP4; 78USP4086236; 79MI3; 83-ACH241
- 6-Hydroxy-1,3-dioxolo[4,5-*h*]quinoline-7-carboxylates:** 69FRP2002-888; 79JMC1354
- 9-Hydroxy-1,3-dithiolo[4,5-*f*]quinoline-8-carboxylates:** 86M1339
- 8-Hydroxy-1,3-dithiolo[4,5-*g*]quinoline-7-carboxylates:** 86M1339
- 4-Oxofuro[3,2-*b*]pyrido[1,2-*a*]pyrimidine-3-carboxylates:** 84CPB4914
- 4-Hydroxyfuro[3,2-*b*]-1,8-naphthyridine-3-carboxylates:** 84CPB4914
- 8-Hydroxyfuro[2,3-*g*]-1,5-naphthyridine-7-carboxylates:** 77MI6
- 4-Oxopyrimido[1,2-*b*]-1,2-benzisoxazole-3-carboxylates:** 82JAP(K)-158789
- 4-Oxopyrimido[1,2-*b*]benzoxazole-3-carboxylates:** 72JMC1203; 73-CPB2019; 79JOC1811
- 9-Hydroxyoxazolo[5,4-*f*]quinoline-8-carboxylates:** 74JAP(K)72297
- 4-Oxopyrimido[2,1-*b*]benzothiazole-3-carboxylates:** 68SAP7053, 68-YZ1003; 72JMC1203; 73CPB2019, 73GEP2241241, 73JHC769; 79JOC-1811; 81FRP2470132
- 9-Hydroxythiazolo[4,5-*f*]quinoline-8-carboxylates:** 74JAP(K)88882
- 9-Hydroxythiazolo[5,4-*f*]quinoline-8-carboxylates:** 71GEP2056224, 71GEP2119396; 73JAP(K)23800; 75GEP2449544, 75JAP(K)46698, 75-JAP(K)52094, 75JAP(K)64298; 76CPB130, 76CPB1050
- 9-Hydroxyisothiazolo[4,3-*f*]quinoline-8-carboxylates:** 73JAP(K)61-500; 74JAP(K)18893; 75JAP(K)84596
- 8-Hydroxyisothiazolo[5,4-*g*]quinoline-7-carboxylates:** 74JAP(K)75596
- 8-Hydroxythiazolo[4,5-*g*]quinoline-7-carboxylates:** 75JAP(K)46698; 76CPB1050; 77JAP(K)83596, 77JAP(K)125196; 79CPB1

- 8-Hydroxythiazolo[5,4-*g*]quinoline-7-carboxylates:** 77JAP(K)125196; 79CPB1
- 6-Hydroxythiazolo[4,5-*g*]quinoline-7-carboxylates:** 77JAP(K)83596, 77JAP(K)125196; 79CPB1
- 4-Hydroxydipyrido[1,2-*b*:3',2'-*d*]pyrazole-3-carboxylates:** 77JAP(K)-17497, 77JAP(K)36695
- 4-Hydroxydipyrido[1,2-*a*:3',2'-*d*]imidazole-3-carboxylates:** 81JHC-1565
- 4-Oxopyrimido[1,2-*b*]indazole-3-carboxylates:** 76T493; 78GEP2822-124; 80MI3
- 4-Oxopyrimido[2,1-*b*]benzimidazole-3-carboxylates:** 51BSB69; 72-JMC230; 73CPB2019, 73JCS(P1)1588, 73JHC71; 78USP4072679, 78USP-4109087, 78USP4109091; 79JOC1811
- 9-Hydroxypyrazolo[3,4-*f*]quinoline-8-carboxylates:** 77JHC1175; 78-GEP2822124, 78JAP(K)119895, 78JAP(K)124299, 78YZ1158; 79USP-4160093; 80MI3; 83JHC1351; 84MI2
- 9-Hydroxypyrazolo[4,3-*f*]quinoline-8-carboxylates:** 78GEP2822124, 78YZ1063; 79JAP(K)32496; 80MI3
- 5-Hydroxypyrazolo[4,3-*g*]quinoline-6-carboxylates:** 78YZ1158; 79-JAP(K)84596
- 4-Hydroxypyrazolo[3,4-*h*]quinoline-3-carboxylates:** 78GEP2822124; 80MI3
- 6-Hydroxypyrazolo[4,3-*h*]quinoline-7-carboxylates:** 78GEP2822124; 80MI3
- 9-Hydroxyimidazo[4,5-*f*]quinoline-8-carboxylates:** 75JHC1319; 79-JAP(K)144398; 80JAP(K)28920; 82MI1; 86EUP187705; 87CCC2918; 88MI11
- 8-Hydroxyimidazo[4,5-*g*]quinoline-7-carboxylates:** 78JAP(K)50197; 89KFZ692
- 6-Oxopyrido[3',2':4,5]thiazolo[3,2-*a*]pyrimidine-7-carboxylates:** 73-JHC769; 74JAP(K)15498
- 9-Hydroxy-1,2,5-thiadiazolo[3,4-*f*]quinoline-8-carboxylates:** 74JAP-(K)15498
- 6-Hydroxy-1,2,5-thiadiazolo[3,4-*h*]quinoline-7-carboxylates:** 76KG-S61; 84MI2

- 6-Hydroxypyrazolo[1,5-*a*]pyrido[3,2-*e*]pyrimidine-7-carboxylates:** 77-
GEP2650780
- 4 - Hydroxypyrido[2',3':3,4]pyrazolo[1,5 - *a*]pyrimidine - 3 - carboxylates:**
77IJC(B)349
- 9-Hydroxypyrazolo[3,4-*f*]-1,7-naphthyridine-8-carboxylates:** 81MI1
- 9-Hydroxypyrazolo[4,3-*f*]-1,7-naphthyridine-8-carboxylates:** 81MI1
- 9-Hydroxy-1,2,3-triazolo[4,5-*f*]quinoline-8-carboxylates:** 87CCC2918;
88MI11; 89FES619
- 4-Oxocyclohepteno(*g*)thiazolo[3,2-*a*]pyrimidine-3-carboxylates:** 81-
FRP2470132
- 4-Oxocycloocteno(*g*)thiazolo[3,2-*a*]pyrimidine-3-carboxylates:** 81-
FRP2470132
- 8-Oxopyrazolo[5,4-*d*:2,3-*a'*]dipyrimidine-7-carboxylates:** 89JCR(S)-
333
- 4-Hydroxybenzo(*f*)quinoline-3-carboxylates:** 39JA2890; 46JA1327;
54JA2429; 67USP3324003, 67USP3324135; 72HCA1319
- 4-Hydroxybenzo(*g*)quinoline-3-carboxylates:** 67JOC3210; 69SAP-
5212; 70GEP1912944
- 4-Hydroxybenzo(*h*)quinoline-3-carboxylates:** 46JA1327; 48JCS893; 58-
MI3; 67JOC3210; 69SAP5212; 70GEP1912944; 71JHC357; 72HCA1319;
74JMC137
- 1-Oxobenzo[*i j*]quinoline-2-carboxylates:** 73GEP2264163; 74GEP24-
15763; 76MIP3, 76USP3969463, 76USP3976651, 76USP3985753, 76USP-
3985882; 77USP4001243, 77USP4014877; 79GEP2914218, 79GEP2914258;
80JAP(K)38364, 80JAP(K)145612, 80JAP(K)149284; 81BEP885605, 81-
FRP2463771, 81FRP2476079, 81JAP(K)55388, 81JAP(K)59773; 82BEP-
891046, 82BEP891537; 83EUP79162, 83JAP(K)90511, 83USP4380543,
83USP4404207, 83USP4416884; 84EUP101829, 84EUP109284, 84EUP-
109285, 84EUP119779, 84NEP1115, 84USP4443447; 85USP4524148;
86EUP203795, 86MI14, 86USP4565872; 87EUP245913, 87JMC839
- 7-Oxopyrido[1,2,3-*de*]benzoxazine-6-carboxylates:** 75USP3883522;
82EUP47005, 82JAP(K)203085; 83JAP(K)29789, 83JAP(K)52290; 84-
CPB4907, 84EUP101829, 84JAP(K)122493, 84JAP(K)216890, 84USP-
4443447; 85JAP(K)126290; 86EUP184384, 86EUP206283, 86JAP(K)-
204188, 86JAP(K)246172, 86JAP(K)246188

- 1-Hydroxy-[1]benzopyrano[3,4-*b*]pyridine-2-carboxylates:** 77JHC-1009; 80USP4210758; 81JHC697
- 4-Hydroxy-[1]benzopyrano[2-3-*b*]pyridine-3-carboxylates:** 78USP-4117134; 81JHC697
- 4-Hydroxy-[1]benzopyrano[3,2-*b*]pyridine-3-carboxylates:** 78USP-4066655; 81JHC697
- 9-Hydroxypyran[3,2-*f*]quinoline-8-carboxylates:** 67USP3313818
- 9-Hydroxypyran[2,3-*g*]quinoline-8-carboxylates:** 70GEP1936393; 72-BRP1283900
- 6-Hydroxypyran[3,2-*g*]quinoline-7-carboxylates:** 70GEP1936393; 72-BRP1283900; 80GEP2943658
- 4-Hydroxybenzothiopyran[3,2-*b*]pyridine-3-carboxylates:** 85JHC89
- 7-Oxopyrido[1,2,3-*de*]-1,4-benzothiazine-6-carboxylates:** 82JAP(K)-203085; 85JAP(K)208987; 87JMC465, 87USP4636506
- 7-Oxopyrido[1,2,3-*de*]quinoline-6-carboxylates:** 82JAP(K)203085, 82USP4348521; 87USP4636506
- 4-Hydroxy-1,7-phenanthroline-3-carboxylates:** 54JA1109; 59MI3; 72-GEP2220294; 74JAP(K)55698; 80JAP(K)69582; 83JHC681; 84MI4
- 10-Hydroxy-2,7-phenanthroline-9-carboxylates:** 81EUP27904
- 1-Hydroxy-4,7-phenanthroline-2-carboxylates:** 49JCS1017
- 4-Hydroxy-1,8-phenanthroline-3-carboxylates:** 83HCA620
- 4-Hydroxy-1,10-phenanthroline-3-carboxylates:** 46JA1320; 59MI3; 62-JOC3878; 72GEP2220294, 72JMC1203; 78USP4123536; 83JHC681
- 9-Hydroxypyrido[2,3-*g*]quinoline-8-carboxylates:** 78JAP(K)28196
- 4-Hydroxypyrido[3,2-*g*]quinoline-3-carboxylates:** 72GEP2220294; 88M761
- 4-Hydroxybenzo[*g*]-1,5-naphthyridine-3-carboxylates:** 50JOC1224; 72JAP35919
- 4-Hydroxybenzo[*h*]-1,6-naphthyridine-3-carboxylates:** 50JOC1224; 58JCS828; 70JMC230
- 4-Oxopyrimido[1,2-*b*]isoquinoline-3-carboxylates:** 83KGS1279; 84-KFZ931; 88MI9

- 4-Oxopyrimido[2,1-*a*]isoquinoline-3-carboxylates:** 78USP4127720;
84JAP(K)172472; 85EUP143001
- 4-Oxopyrimido[1,2-*a*]quinoline-3-carboxylates:** 71IJC201; 72JMC-
1203; 74MIP1; 75GEP2513930; 77GEP2628751, 77GEP2630469, 77USP-
4031217; 78GEP2801248, 78YZ1279; 79MIP1, 79USP4175193; 84S152
- 4-Hydroxycyclohepta[4,5]pyrrolo[2,3-*b*]pyridine-3-carboxylates:** 87-
BCJ1053
- 4-Oxocyclohepta[4,5]pyrrolo[1,2-*a*]pyrimidine-3-carboxylates:** 87-
BCJ1053
- 10-Hydroxy-1,3-dioxino[4,5-*f*]quinoline-9-carboxylates:** 72MI4, 72MI5
- 10-Hydroxy-1,3-dioxino[5,4-*f*]quinoline-9-carboxylates:** 72GEP213-
9212, 72MI4
- 9-Hydroxy-1,3-dioxino[4,5-*g*]quinoline-8-carboxylates:** 70GEP193-
6393; 72BRP1283900, 72CR(D)1583, 72GEP2139212, 72MI5
- 6-Hydroxy-1,3-dioxino[5,4-*g*]quinoline-7-carboxylates:** 72MI5; 77JA-
P(K)142098
- 4-Hydroxy-1,3-dioxino[4,5-*h*]quinoline-3-carboxylates:** 72MI5
- 7-Hydroxy-1,3-dioxino[5,4-*h*]quinoline-8-carboxylates:** 72MI5
- 9-Hydroxy-1,4-dioxino[2,3-*f*]quinoline-8-carboxylates:** 81JOC3846
- 9-Hydroxy-1,4-dioxino[3,2-*g*]quinoline-8-carboxylates:** 69FRP200-
2888, 69GEP1814187; 70GEP1936393; 72BRP1283900; 73GEP2303496,
73JAP(K)6479; 75KGS1663; 76JMC982; 81JOC3846
- 9-Hydroxypyrido[3,2-*g*]-1,4-benzoxazine-8-carboxylates:** 78JAP(K)-
28196
- 10-Hydroxy-1,4-oxazino[3,2-*f*]quinoline-9-carboxylates:** 88IJC(B)649
- 9-Hydroxy-1,4-oxazino[2,3-*g*]quinoline-8-carboxylates:** 88IJC(B)649
- 1-Oxopyrimido[2,1-*c*]-1,4-benzoxazine-2-carboxylates:** 81USP42-
54118
- 10-Hydroxy-1,4-thiazino[2,3-*f*]quinoline-9-carboxylates:** 84MI5
- 10-Hydroxy-1,4-thiazino[3,2-*f*]quinoline-9-carboxylates:** 84MI5
- 9-Hydroxy-1,4-thiazino[2,3-*g*]quinoline-8-carboxylates:** 84MI5
- 6-Hydroxy-1,4-thiazino[3,2-*g*]quinoline-7-carboxylates:** 84MI5

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| 7-Hydroxy-1,4-thiazino[2,3-<i>h</i>]quinoline-8-carboxylates: | 84M15 |
| 8-Hydroxy-1,4-thiazino[3,2-<i>h</i>]quinoline-7-carboxylates: | 84M15 |
| 1-Oxopyrimido[2,1-<i>c</i>]-1,4-benzothiazine-2-carboxylates: | 81USP-4254118 |
| 10-Hydroxypyrazino[2,3-<i>f</i>]quinoline-9-carboxylates: | 78JAP(K)-147095; 79GEP2833018 |
| 7-Hydroxypyrido[3,2-<i>h</i>]cinnoline-8-carboxylates: | 51JOC1414 |
| 1-Hydroxypyrido[3,2-<i>b</i>]-1,5-naphthyridine-3-carboxylates: | 78BAP509 |
| 7-Hydroxypyrido[3,2-<i>c</i>]-1,5-naphthyridine-8-carboxylates: | 59JA6297 |
| 10-Hydroxypyrido[3,2-<i>f</i>]-1,7-naphthyridine-9-carboxylates: | 78YZ-1279 |
| 10-Hydroxypyrido[3,2-<i>f</i>]quinoline-9-carboxylates: | 78JAP(K)147095; 79GEP2833018 |
| 4-Oxopyrimido[2,1-<i>a</i>]phthalazine-3-carboxylates: | 74CR(C)209 |
| 1-Oxopyrimido[1,2-<i>a</i>]quinazoline-2-carboxylates: | 89JHC161 |
| 4-Oxopyrimido[1,2-<i>c</i>]quinazoline-3-carboxylates: | 81EUP30156; 86-JAP(K)50983 |
| 1-Oxopyrimido[1,2-<i>a</i>]quinoxaline-2-carboxylates: | 77JCS(P1)789 |
| 1-Oxopyrimido[1,2-<i>a</i>]-1,5-naphthyridine-2-carboxylates: | 78MI7 |
| 10-Oxopyrimido[1,2-<i>a</i>]-1,6-naphthyridine-9-carboxylates: | 74JHC151 |
| 10-Oxopyrimido[1,2-<i>a</i>]-1,8-naphthyridine-9-carboxylates: | 67G1274; 69G677; 71G129, 71JCS(C)2985; 72G253 |
| 4-Hydroxyanthryridine-3-carboxylates: | 67G1274; 69G677; 71G129 |
| 4-Oxopyrimido[1,2-<i>b</i>]-1,2,4-benzothiadiazine-3-carboxylates: | 89JHC-473 |
| 7-Oxopyrido[1,2,3-<i>ef</i>]-1,5-benzoxazepine-6-carboxylates: | 82JAP-(K)203085 |
| 10-Hydroxy-1,4-dioxepino[2,3-<i>g</i>]quinoline-9-carboxylates: | 69GEP-1814187 |
| 1-Oxopyrimido[1,2-<i>a</i>]-1,4-benzodiazepine-2-carboxylates: | 74GEP-2400449 |
| 5-Oxo-1,3-dioxolo[4,5-<i>g</i>]thiazolo[3,2-<i>a</i>]quinoline-4-carboxylates: | 82-EUP58392 |

9-Oxo-1,3-dioxolo[4,5-*f*]pyrido[2,1-*b*]benzothiazole-8-carboxylates: 73-JHC769

4-Oxopyrimido[1,2':1,5]-1,2,4-triazolo[3,4-*b*]benzoxazole-3-carboxylates: 89H925

1-Hydroxyindeno[2,1-*f*]quinoline-2-carboxylates: 51JA1844

4-Oxopyrido[3,2,1-*gh*]carbazole-5-carboxylates: 79GEP2849158, 79-GEP2914218, 79GEP2914258; 80JAP(K)145612

7-Oxo-1*H*,7*H*-benzofuro[4,5,6-*ij*]quinolizine-6-carboxylates: 79-JAP(K)163598; 84CPB4923

4-Hydroxybenzofuro[3,2-*h*]quinoline-3-carboxylates: 69GEP1908542; 70GEP2021100; 71BRP1240446

7-Oxo-1*H*,7*H*-[1]benzothieno[4,5,6-*ij*]quinolizine-6-carboxylates: 79JAP(K)163598

7-Oxo-1*H*,7*H*-[1]benzothieno[5,6,7-*ij*]quinolizine-6-carboxylates: 88AP241

4-Hydroxypyrido[2,3-*a*]carbazole-3-carboxylates: 52JOC1501

1-Hydroxypyrido[2,3-*c*]carbazole-2-carboxylates: 52JOC1501; 87FES-641

4-Hydroxypyrido[3,2-*b*]carbazole-3-carboxylates: 52JOC1501; 87CPB-425

10-Hydroxyindolo[4,3-*fg*]quinoline-9-carboxylates: 39JA2890

7-Oxo-(1,3)-benzodioxolo[4,5,6-*ij*]quinolizine-6-carboxylates: 73G-EP2264163; 76USP3969463; 77USP4001243, 77USP4014877

1-Oxo-(1,3)-benzodioxolo[4,5,6-*ij*]quinoline-2-carboxylates: 73G-EP2264163; 76USP3969463; 77USP4001243, 77USP4014877

7-Oxofuro[2,3-*h*]pyrido[1,2,3-*de*]-1,4-benzoxazine-6-carboxylates: 84CPB4923

11-Oxonaphtho[1',2':4,5]thiazolo[3,2-*a*]pyrimidine-10-carboxylates: 68SAP7053; 72JMC1203; 85AP84

8-Oxonaphtho[2',1':4,5]thiazolo[3,2-*a*]pyrimidine-9-carboxylates: 68SAP7053

1-Oxobenzimidazolo[4,5,6-*ij*]quinazoline-2-carboxylates: 79JAP(K)-154797

4-Oxopyrimido[1',2':1,6]pyrido[3,4-*b*]indole-3-carboxylates: 87MIP4

11-Hydroxypyrido[3,2-*g*]thiazolo[3,4,5-*de*]quinoxaline-10-carboxylates:
78JAP(K)28196

4-Oxopyrimido[1,2-*a*]pyrrolo[2,1-*c*]-1,4-benzodiazepine-3-carboxylates:
85CPI197242, 85JHC305

4-Hydroxynaphtho[1,2-*f*]quinoline-3-carboxylates: 54JPJ203

1-Hydroxynaphtho[2,3-*f*]quinoline-2-carboxylates: 62MI2

4-Hydroxynaphtho[2,3-*h*]quinoline-3-carboxylates: 59MI2

7-Oxonaphtho[1,2,3-*i,j*]quinolizine-6-carboxylates: 84USP4456606

4-Hydroxypyrido[2,3-*c*]acridine-3-carboxylates: 77JAP(K)3099, 77-USP4060527

7-Oxopyrido[1,2,3-*de*]-4,7-phenanthroline-6-carboxylates: 88M761

7-Oxopyrido[3,2,1-*gh*]-1,7-phenanthroline-6-carboxylates: 88M761

4-Hydroxybenzo(*f*)-1,7-phenanthroline-3-carboxylates: 72GEP222-0294

4-Oxoisoquinoline[4,5-*g*]quinoline-3-carboxylates: 86IJC(B)652

1-Oxo-1,4-benzodioxino[5,6,7-*ij*]quinolizine-2-carboxylates: 73G-EP2264163; 76USP3969463; 77USP4001243, 77USP4014877

4-Hydroxypyrido[2,3-*b*]phenothiazine-3-carboxylates: 79JAP(K)30198

11-Oxopyrimido[1,2-*a*]perimidine-10-carboxylates: 89AP303

4-Hydroxypyrido[2,3-*b*]anthrydine-3-carboxylates: 74FES366

4,9-Dioxodipyrimido[1,2-*a*:1',2'-*c*]quinazoline-3,8-dicarboxylates:
81EUP30156

4-Oxodibenzo(*c,f*)pyrimido[1,2-*a*]azepine-3-carboxylates: 80JHC341

2-Oxodibenzo(*c,f*)pyrimido[1,2-*a*]azepine-3-carboxylates: 80JHC341

4-Oxodibenzo(*b,f*)pyrimido[1,2-*d*]-1,4-thiazepine-3-carboxylates: 80-JHC341

4,11-Dihydroxybenzo[1,2-*h*:4,5-*h'*]diquinoline-3,10-dicarboxylates: 62-MI2

4,10-Dihydroxybenzo[1,2-*h*:5,4-*h'*]diquinoline-3,11-dicarboxylates:
59MI2

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